LECTURES

IN

MEDICAL BIOCHEMISTRY

BY

Prof. Dr. FAROUK HUSSEIN SABER

PROFESSOR AND HEAD OF MEDICAL

BIOCHEMISTRY – FACULTY OF MEDICINE

AL-AZHAR UNIVERSITY

CAIRO – EGYPT

FOR

MEDICAL STUDENTS – POST GRADUATES AND

DENTAL STUDENTS

PART II

2006 – 2007

Contents

Carbohydrates Metabolism

Dietary Carbohydrate Staffs :

I - Polysaccharides :

a) Starch :

Rich sources are potatoes, rice, corn and wheat.

b) Cellulose :

Is constituent of plant cell wall (B. glucose Polymer), not digested, and passes as such in intestine → increases Bulk of stool → prevents constipation.

II – Disaccharides :

a) Sucrose :

(Cane sugar; table sugar), present in sugar cane and beet roots.

b) Maltose :

Presents in malt, and produced by amylase digestion of starch in intestine.

c) Lactose : (milk sugar)

Presents in milk, is the main source of galactose.

II – Monosaccharide :

a) Glucose : (grape sugar)

Present in fruit juice, is product of other carbohydrates digestion .

b) Fructose : (honey sugar)

Present in fruit juice, produced by hydrolysis of sucrose .

The aim of carbohydrates digestion, absorption, and metabolism is to extract. Its solar energy during its formation in plants by photosynthesis :

In plant → [CO_2 + H_2O + external Solar Energy $\xrightarrow{Photosynthesis}$ carbohydrates + O_2]

In human → [carbohydrates $\xrightarrow[O_2]{Metabolism}$ CO_2 + H_2O + intracellular energy]

Digestion :

In Mouth :

Starch is hydroysed by salivary amylase (PH 6.7, CL) to release amylodextrin → erythro. dext. → amylo.dext → maltose , according to time of mastication.

In Stomach :

Stomach acidity inhibits salivary amylase → no digestion of carbohydrates.

In Small intestine :

a) Pancreatic amylase (PH 7.0) completes starch digestion into maltose.

b) Intestinal disaccharides :

Complete carbohydrate digestion into monosaccharide as follows :

- Maltose $\xrightarrow{Maltase}$ 2 glucose
- sucrose $\xrightarrow{Sucrase}$ glucose + fructose
- Lactose $\xrightarrow{Lactase}$ glucose + galactose

So, the end products are mainly glucose, fructose and galactose, the latter two are changed into glucose in the liver

Disorders of carbohydrates digestion :

1- Inherited lactose intolerance (Lactase deficiency):

It starts early in infants with lactation, they complain of abdominal distension and colic, may diarrhea due to fermentation of unabsorbed lactose by intestinal bacteria.

2- Inherited sucrase deficiency:

It starts later in infants when add sucrose to the infant diet, also it produces abdominal distension and colic.

Absorption :

Monosaccharide can be absorbed (transported) by two different mechanisms :

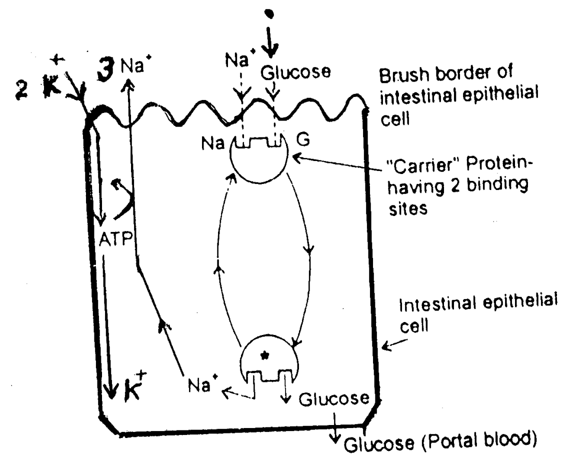
1- Simple diffusion (passive transport):

- It is mainly for fructose and pentosis.
- sugars pass from high to low concentration, with concentration gradient, it needs no energy.
- Diet pentosis are not utilized in our body due to deficiency of the pentokinase enzyme.

2- Active transport:

- It is mainly for glucose, galactose and mannose.
- Sugars pass from low to high concentration (against concentration gradient), it needs energy from ATP.
- In intestinal cell membranes there is a mobile carrier which binds both glucose and Na+, then they separate in Cytosol.

- The carrier gets back to cell membrane, also Na+ is pumped again (by Na+/K+ pump) to cell membrane with aid of ATP to carry glucose once more.
- Inside body, glucose transport in red cells, liver, pancreatic B. cells, brain and small intestine is insulin independent, also fructorse is insulin independent.
- Glucose transport in heart, skeletal muscles, adipose tissue and kidney is insulin dependent.



'CARRIER PROTEIN' AND TRANSPORT OF GLUCOSE

Fate of Absorbed Sugars

I – Uptake by liver :

- Glucose, fructose and galactose are transported by portal blood to liver where fructose and galactose are changed into glucose which is transported to all body cells by systemic blood.

II – Utilization by tissues :

A) Oxidation : (50% of absorbed glucose)

i- Major pathway : is mainly for energy production.

a) Glycolysis : Produces less amount of energy.

b) Citric acid cycle : Produces maximum amount of energy.

ii) Minor pathway : no energy, but important compounds.

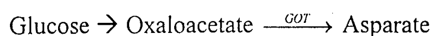
a) Hexose monophashate pathway (HMP) → Pentosis, NADP2H

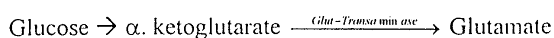
b) Uronic acid pathway → Glucouronic acid

B) Conversion to important compounds : Glucose gives rise to :

- Pentosis in liver, RBCS, and adipose tissues by HMP for DNA & RNA formation.
- Fructose in semen.
- Galactose in mammary gland.
- Glucouronic acid in liver.
- Amins acids by transamination.







C) **Storage :**

- Excess dietary carbohydrates can be stored as liver and muscle glycogen (about 10% of absorbed glucose) or stored in adipose tissues as subcutenaes fat (30 – 40 % of absorbed glucose)

III – Excretion :

Excess blood glucose is excreted in urine if exceeds the renal thresholds (above 180 mg%).

Major pathway for Glucose Oxidation

I – Occurs in every cell to supply energy, it is divided into two stages :

i) Anaerobic stage (glycolysis), followed by

ii) Aerobic stage (citric acid cycle)

Glycolysis
(Embden Meyerhof Pathway)

Is Oxidation of glucose to pyruvic acid in presence of relatively oxygen, it occurs in cytoplasm of all tissue cells or oxidation of glucose into lactic acid in absence of oxygen, it occurs during muscular exercise or in R.B.cs (has no mitochondria).

- **Steps : Glycolysis has two stages :**

Stage I :

Glucose is converted into two moles of glyceraldhyde-3.p (in which 2 ATP moles are utilized).

Stage 2 :

The two moles of glyceraldhyde-3.p are converted into two moles of pyruvate (under aerobic condition) or loctate (under amerobic condition), in which 10 ATP moles are produced in this stage.

Glucokinase :

Present in liver, acts on glucose, has low affinity to glucose (acts in high blood glucose level), is insulin dependent.

Hexokinase:

Present extrahepatic, acts on glucose, fructose, has high affinity to glucose (acts on low level of blood glucose), is insulin independent.

Differences between "*hexokinase*" and "*glucokinase*"

Hexokinase	*Glucokinase*
1. Non-specific, can phosphorylate any of the hexoses	1. Specific, can phosphorylate glucose only
2. More stable	2. Physiologically more labile
3. Found almost in all tissues	3. Found only in liver
4. Found in foetal as well as in adult liver	4. Found in adult liver, not in foetal liver
5. Allosteric inhibition by glucose-6-P	5. Not inhibited by Glucose-6-P
6. Km is low = 0.1 mM, hence high affinity for glucose	6. Km is high = 10 mM, low affinity for glucose
7. Not very much influenced by diabetic state/or fasting	7. Depressed in fasting and in diabetes. Glucokinase is deficient in patients of DM, changes according to nutritional status
8. No change with glucose feeding	8. Increased by feeding of glucose after fasting
9. Inhibited by glucocorticoids and GH; insulin does not have effect on hexokinase	9. Inhibited by glucocorticoids and GH; glucose and insulin stimulates. Synthesis is induced by insulin, an ***Inducible enzyme***
10. Hexokinase activity of liver found in three enzyme proteins (isoenzymes)	10. Not known
11. Main function to make available glucose to tissues for oxidation at lower blood glucose level	11. *Main function to clear glucose from blood after meals and at blood levels greater than 100 mg/dl*

GLYCOLYSIS
Or
Embden – Meyerhof – Parnas – Pathway

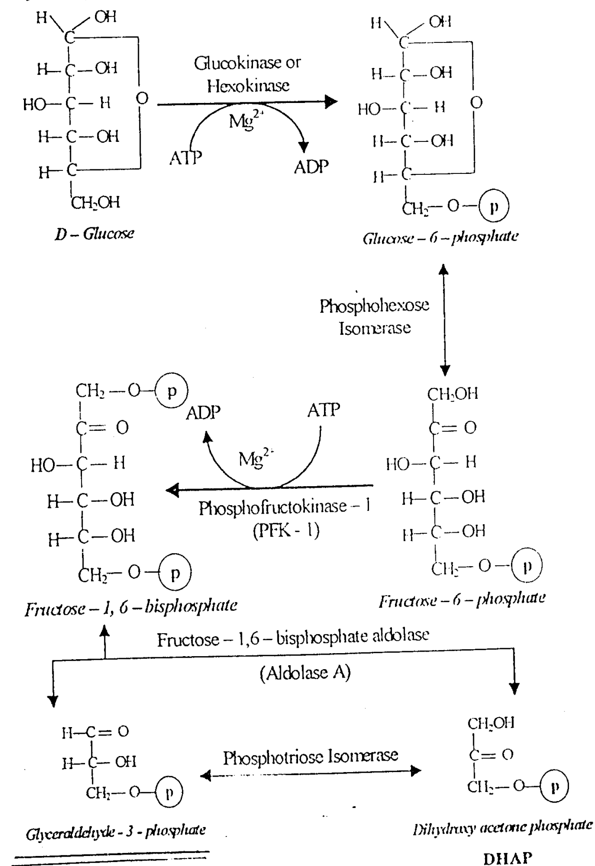
It is a series of biochemical reactions by which glucose is converted to pyruvate in aerobic condition or converted to lactate in anaerobic condition.

Site and Steps

The enzymes of glycolysis are present in the cytosol of all cells.

The steps of glycolysis can be classified into two phases:

I- Phase one: In this phase glucose is converted into two molecules of glyceraldehyde-3-phosphate.



II- Phase two: in this phase the two molecules of glyceraldehyde-3-phosphate are converted into two molecules of **pyruvate (aerobic) or lactate (anaerobic).**

(2) $H-C=O$ / $H-C-OH$ / $CH_2-O-(P)$

Glyceraldehyde - 3 - phosphate

2 Pi

2 NAD^+

Glyceraldehyde -3- Phosphate dehydrogenase

2 $NADH.H^+$

(2) $COO-(P)$ / $H-C-OH$ / $CH_2-O-(P)$

1,3 - bisphosphoglycerate (BPG)

Mg^{2+}

2 ADP

Phosphoglycerate kinase

2 ATP

(2) COOH / $H-C-OH$ / $CH_2-O-(P)$

3 - Phosphoglycerate

Phosphoglycerate mutase

(2) COOH / $H-C-O-(P)$ / CH_2-OH

2 - phosphoglycerate

H_2O

Enolase

Mg^{2+}

(2) COOH / $C-O-(P)$ / CH_2

2 - phospho enol pyruvate (2-PEP)

2 ATP

Mg^{2+}

Pyruvate kinase

2 ADP

(2) COOH / $C-OH$ / CH_2

Enol - pyruvate

Spontaneous

(2) COOH / $C=O$ / CH_3

Keto - pyruvate

Lactate dehydrogenase (LDH)

(2) COOH / C HOH / CH_3

Lactate

ATP Production of Glycolysis

Glucose

ATP

ADP

G - 6 - (P)

F - 6 - (P)

ATP

ADP

F - 1,6 – bisph.

(2) *Glyceraldehyde - 3 - (P)*

2 NAD^+

2 $NADH.H^+$

ETC

6 ATP

(2) *1,3 - BPG*

2 ADP

2 ATP

(2) *3 - Phosphoglycerate*

(2) *2 - PEP*

2 ADP

2 ATP

(2) *Pyruvate*

8 ATP

Importance of Glycolysis

I – Energy Production :

a) Under aerobic Condition :

[Glucose → 2 Pyrnvate + 8 ATP]

- Two moles of NADH are produced by reaction of glyceraldehydes -3.p → 1.3 bisphoshoglycerate, where the two NADH give rise to 6 ATP in respiratory chain.
- Two moles of ATP are produced in reaction of 2-ph. Enol. Pyruvate → enol pyruvate.
- So, the total amount of energy equals 10 ATP, and there is two utilized ATP, so the net energy is 8 ATP.

b) Under anerobic Condition : (muscular exercise and RBcs)

[glucose → 2 Lactate + 2 ATP]

- The two produced NADH as in aeobic condition are utilized in convertion of pyruvate → Lactate, so the net energy is only 2 ATP.
- The two NADH are converted to two oxidized NAD which are required for reaction glyceraldyde -3 -p → 1.3 bisphosphosphoglycerate for continuation of glycolysis , specially in red cells where has no mitochondria to oxidize NADH.

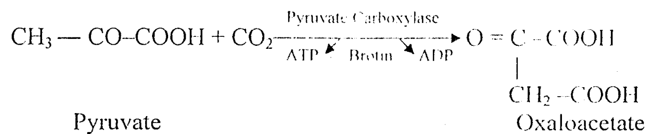
- So, under anaerobic glucose oxidation (muscular exercise or in Red celis → 2 ATP only, but under complete aerobic oxidation → 38 ATP are produced in citric acid cycle.

II – Importance of Glycolytic intermediates :

a) Pyruvate :

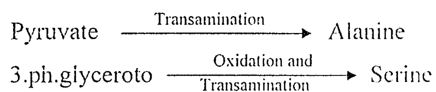
Pyruvate is converted to active acetate which is oxidized in citric acid cycle to give more energy.

- Pyruvate is carboxylated into oxaloacetate which is initiator of citric acid cycle.



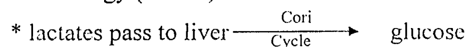
(b) Dihydroxy acetone phosphate can give rise to glycerol -3 -ph, which is utilized for synthesis of triacylgycerol.

(c) Synthesis of amino acids :



III – Importance of Glycolysis in Red cells :

a) **Energy Production :** It is the only pathway to supply the red cells with energy (2 ATP) + Lactate.



b) **Reduction of methemoglobin :**

Glycolysis provides NADH for reduction of useless methemoglobin (oxidized Fe^{+++} Ferric iron) into normal Ferrous Fe^{++} iron.

c) **Hemolytic anemia due to deficiency of glycolytic enzymes :**

* Red cells are dependent on glycolysis for production of ATP, so deficiency of pyruvate kinase (95%) or ph. Hexose isomerase (4%) produces hemolytic anemia.

d) **2,3 bis. Phosphoglycerate cycle (Rapoport- Luebering Cycle) :**

In red cells 1,3 bis.phosphoglycerate is converted to 2.3 bis.phosphoglycerate which combines with Hb causing a decrease in affinity (binding) of Hb to O2 (at low oxygen tension), thus oxygen is released easily to tissues especially in cases of hypoxia.

IV– Reversal of glycolysis (gluconeogenesis):

a) Glycolysis : is reversed for synthesis of glucose from non carbohydrate origin, it is occurred during fasting or low carbohydrate intake .

- **Transport of cytoplasmic NADH (produced in glycolysis) to mitochondria to liberate ATP occurs by two mechanisms (shuttles):**

i) **Malate- aspartate shuttle :**

* Is mechanism to transport NADH to inside mitrochodria to produce 6 ATP :

* 2 cytoplasmic oxaloacetate +2NADH → 2malate → penetrate Mitochondria, and clcavage into 2 oxalacetate + 2 NADH which give rise to 6 ATP in respiratory chain, it occurs in liver and heart muscles. Oxalacetate is converted into aspartate by transamination.

ii) Glycero phosphate shuttle :

* It occurs in certain muscles and nerve cells.
* It gives rise to 4 ATP.

Cytoplasmic di hydroxy acetone-ph + NADH → Glycerol .3- Ph

Glyceral. 3-ph penetrates mitochondria and cleavage into Dihydroxy acetone-p (get back to cytoplasm) and FAD_2H which gives rise to 4 ATP in respiratory chain.

Regulation of Glycolysis

I) Hormonal Regulation

* After meal, excess blood glucose stimulates insulin, which in turn stimulate the three irreversible Key enzymes (Glucokinase, phoshofructo- Kinase, and pyruvate kinase) → stimulation of Glycolysis → decrease excess blood glucose.
* In low blood glucose level, gulcagon is secreted, which in turn inhibits the glycolytic key enzymes → increase blood glucose.

II) Regulation by the energy state of the cell :

* Increase ATP in the cell inhibits both ph. Fructokinase and pyruvate kinase → inhibition of glycolysis
* But increase of ADP & AMP activate the glycolytic key enzymes → Stimulation of glycolysis.

III) Feedback inhibition :

* Glucose-6-p inhibits hexokinase → inhibits glycolysis.
* Citrate inhibits ph. Fnucto kinase → inhibits glycolysis

** The anticoagulant fluoride inhibits glycolysis in blood samples at level of enolase enzyme.

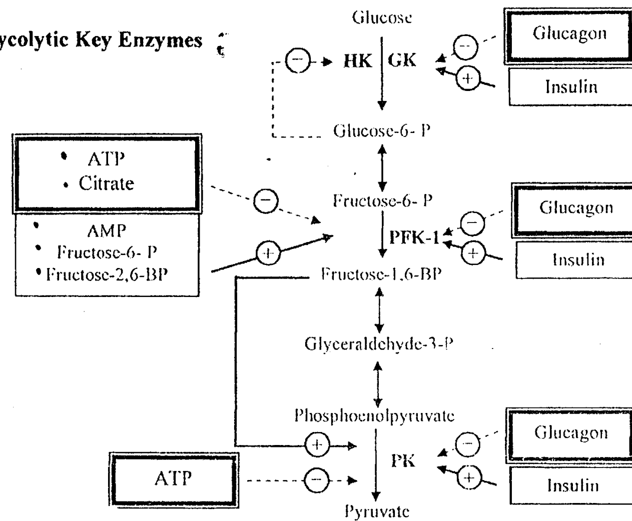
** **Glucokinase**

Present in liner, acts specifically on glucose, stimulated by insulin.

** **Hexokinase :**

Present extrahepatic, acts on glucose & other monosaccharides is insulin independent.

Regulation of Glycolytic Key Enzymes :



- **Lactic acid :** normal level (4 : 16 mgl)

  - Sources :

i) **Physiological :**

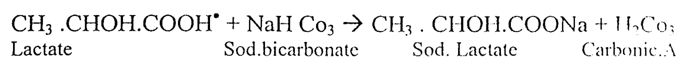
Glycolysis in Red cells, severe muscular exercise .

ii) **Pathological :**

- Blood lactate is increased in anoxia conditions (absence of oxygen → increase (Lactic acid).
- The oral hypoglyce-mic phenformin → lactic acidosis by inhibition of aerobic oxidation, and stimulation of anerobic glucose oxidation.

- **Effects :**

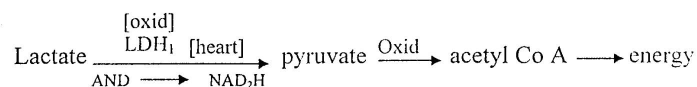
Excess lactate is neutralized by bicarbonate Buffer → Sodium lactate, this leads to depletion of Alkali reserve → lactic acidosis and may coma



- **Fate :**

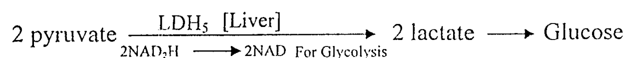
(1) Lactate is converted to pyruvate, then oxidized to give energy, specially in heart muscle through LDH_1.

* **In Heart :**



- LDH_1 has high affinity to lactate.
- But in liver cells, LDH_5 has high affinity to pyruvate, NAD is produced which is important for continuation of glycolysis.

* **In Liver :**



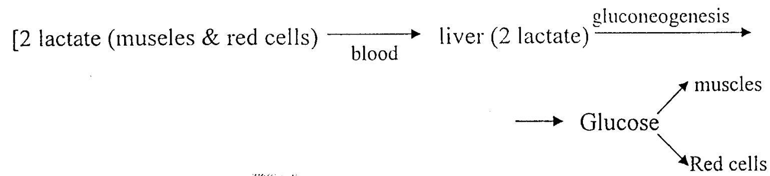
(2) Lactate may accumulate in muscles → Fatigue and pain.

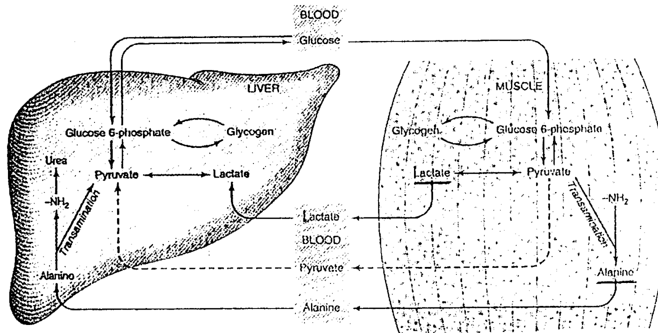
(3) Lactate may excreted in urine and sweat.

(4) Lactate may converted to glucose [Cori- Cycle] to avoid excretion of lactate in urine as waste product.

Cori cycle : (metabolism of lactic acid)

- Lactate is formed during anaerobic oxidation of glucose in red celis and muscles, then diffuses through blood to the liver.
- In liver lactate is converted to pyruvate by LDH and NAD, then pyruvate is converted to glucose via gluconeogenesis, then glucose gets back to red cells and muscles for its utilization.





- Importance of Cori-cycle :

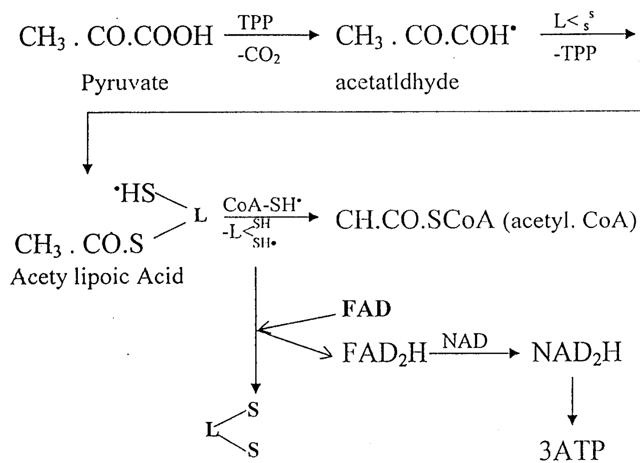
(1) It prevents loss of lactate as waste product in urine.

(2) It maintains blood glucose level.

(3) It supplies red cells and contracting muscles with glucose for reutilization and ATP production.

(4) In liver cells gluconeogenesis consumes its energy from fatty acids oxidation, so glucose is spared to Red cells and contracting muscles to gain energy.

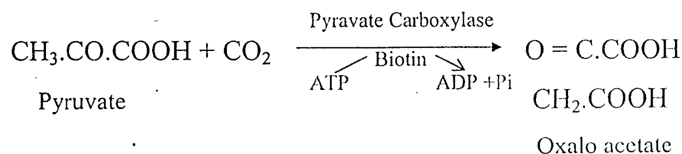
ساقط من أصل المصدر



* Deficiency of TPP (ViT B_1) or pyruvate dehydrogenase enzyme leads to accumulation of pyruvate which is converted into lactate → lactic acidosis, so diabetic patients (suffer from Vit B_1, deficiency) must receive vit B_1. Otherwise Suffer from beri. Beri and peripheral neuritis.

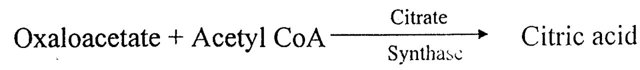
- Also pyruvate may be converted → to oxaloacetate :

Pyruvate in mitochondria my be converted into oxaloactate by carboxylation in presence of pyruvate carboxylase to initiates citric acid cycle.

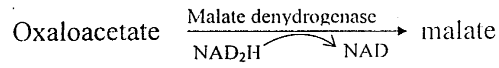


Importance of Oxalocetate :

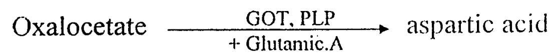
1) Formation of Citric acid :

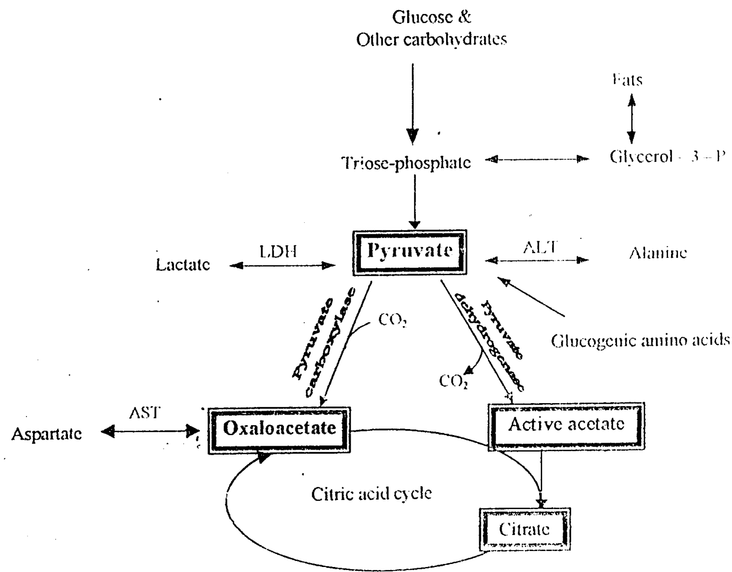


2) Formation of malic acid :



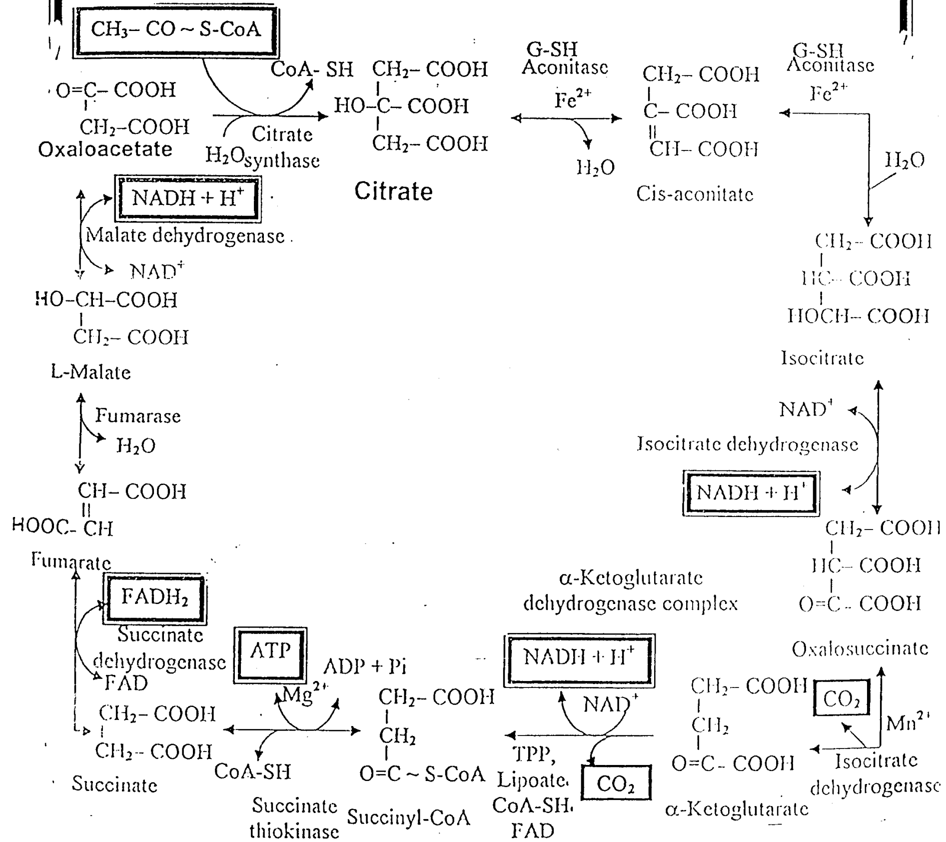
3) Formation of aspartic acid : by transamination.





B- Oxidation of Acetyl CoA in Citric acid cycle; Krebs Cycle

* It is series of biochemical reaction in mitochondria for complete oxidation of acetyl-CoA.
* Citric acid cycle begins by condensation of acetyl-CoA with oxaloacetate to form citrate which is then reconverted to oxalo-acetate through several steps in citric acid cycle.



* **During this process, there is release of :**

a) Two moles of CO_2 [per one mole acetyl.CoA]

b) Three moles of NADH/mole acetyl-CoA → 9ATP in respiratory chain.

* One FAD_2H /mole acetyl CoA→9ATP in respiratory chain.

* One ATP at substrate level.

[Succinyl.CoA $\xrightarrow[\text{thiokinase}]{\text{ADP. Pi}}$ Succinate + Atp + CoA-SH]

c) Release of 12 moles of H_2O during oxidation of NADH & FADH in respiratory chain, (but oxidation of one mole palmitate gives rise to 46 moles of H_2O in resp.Chain)

- **Net energy production :**

So, oxidation of one mole acetyl CoA gives rise to :

9 ATP (3NADH x 3) + 2ATP (1 FAD_2H x 2) + 1 ATP (Substrate level) → 24 ATP

and the two moles of acetyl CoA → 2 ATP

* And as mentioned before oxidation of two moles of pyruvate give rise to 6 ATP.

* Also anerobic oxidation of glucose mole (Glycolysis) gives rise to 8 ATP.

∴ **Net result** : 8 Atp (Glycolysis) + 6 Atp (Pyrvate) + 24 ATP(acetyl.CoA) = 38 ATP/gm mole glucose.

* One mole gram of glucose = its molecular weight = 180 gm glucose → 38 ATP in vivo

* But one gm glucose gives rise to 4.2 K.Cal in vitra.

- Importance of citric acid cycle :

(1) Production of large amounts of energy (30 Atp) .

(2) provides body with succinyl –CoA which is required for heme synthesis.

(3) Provides body with amino acids : by Transamination

* Oxaloacetate → Aspartic acid

* ∝.Keto glutarate → Glutamic acid

(4) Citric acid cycle is the common pool for oxidation of carbohydrates, lipids, and protein to liberate energy through acetyl-CoA.

(5) CO_2 produced in citric acid cycle is used to convert :

pyruvate + CO_2 → oxalo acetate

Ammonia + Atp +CO_2 → Carbamoyl.Ph → Urea formation

* Acetyl.CoA +CO_2 → Malonyl.CoA (Lipogenesis) → Fatty.acid

* Synthesis of H_2CO / $NaHCO_3$ body buffer.

* Synthesis of purine and pyrimidine bases.

Key enzymes : Citrate synthase, isocitrate dehydrogenase, and ∝ .Keto.glut.dehydrogenase.

Regulation :

* Are inhibited by excess ATP, NADH + H^{-}

* Are stimulated by excess ADP.

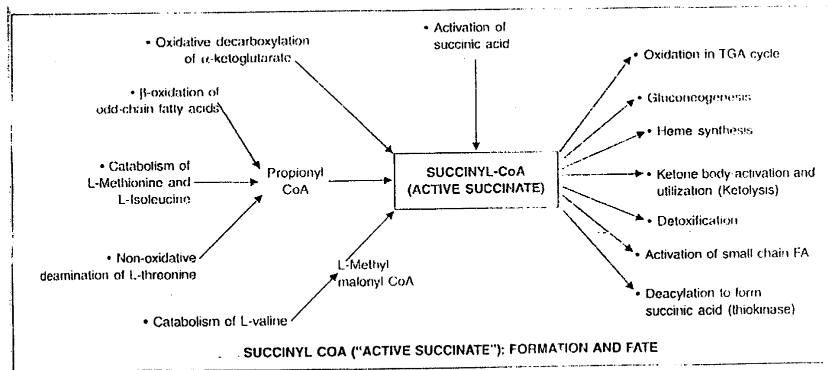
- **Efficiency of TCA Cycle :**

1. Complete oxidation of glucose to CO_2 and H_2O in a 'Bomb calorimeter' yields 686,000 calories which is liberated as heat.
2. When oxidation occurs in tissues, some of this energy is not lost immediately as 'heat' but captured as "high energy PO_4 bonds". At least 38 high energy PO_4 bonds are generated per molecule of glucose oxidized to CO_2 and H_2O.
3. Assuming each high energy bond to be equivalent to 7600 calories. Total energy captured in ATP per mol. of glucose oxidized:

$$= 7,600 \times 38$$
$$= 288,800 \text{ calories}$$

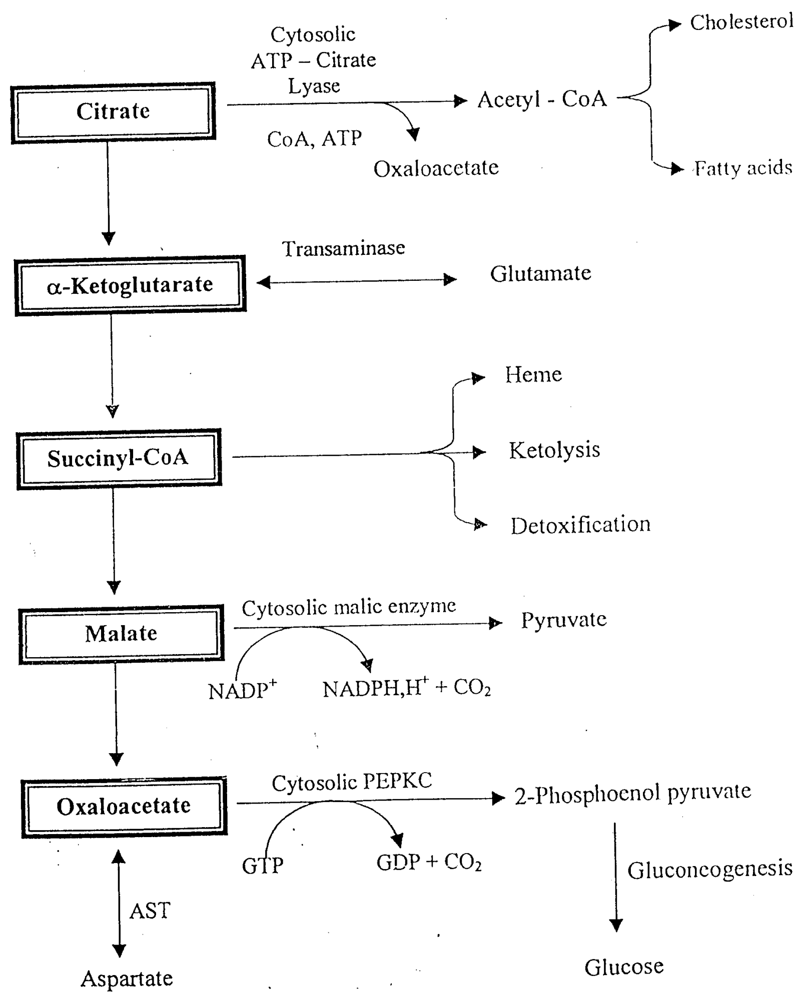
$$\text{Hence, efficiency} = \frac{288,800}{686,000} \times 100$$

= *42% of energy of combustion.*



SUCCINYL COA ("ACTIVE SUCCINATE"): FORMATION AND FATE

Importance of The Intermediates of TCA Cycle



Hexose Monophosphate Pathway

• Is alternative pathway for glucose oxidation, where no energy is produced, but other important products as pentose – P and reduced NADPH + H.

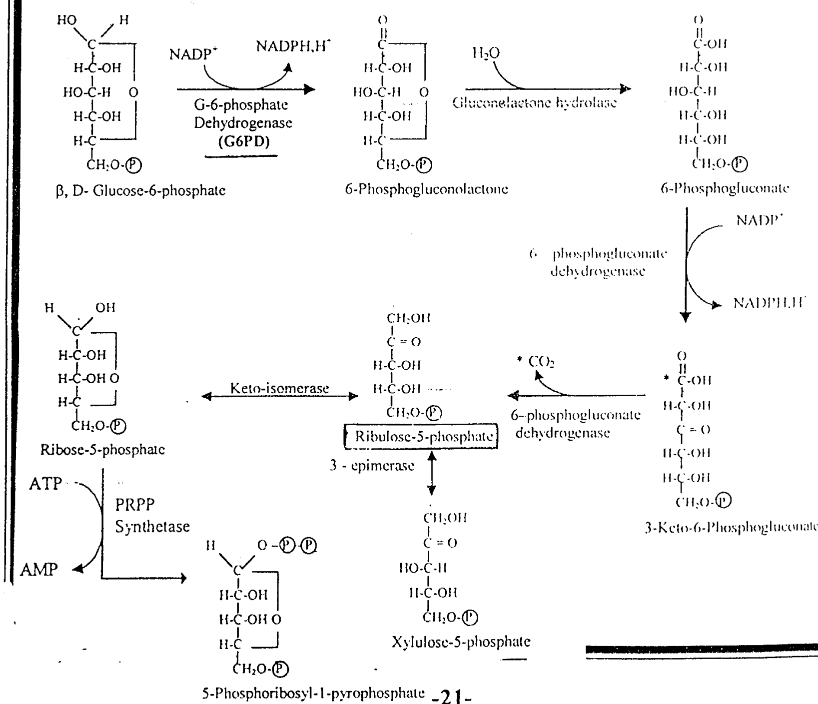
Site

• Cytosol of adipose tissues, mammary gland, liver , adrenals, ovaries, testis and red cells, where reduced NADPH is required

Phases of reaction : two phases

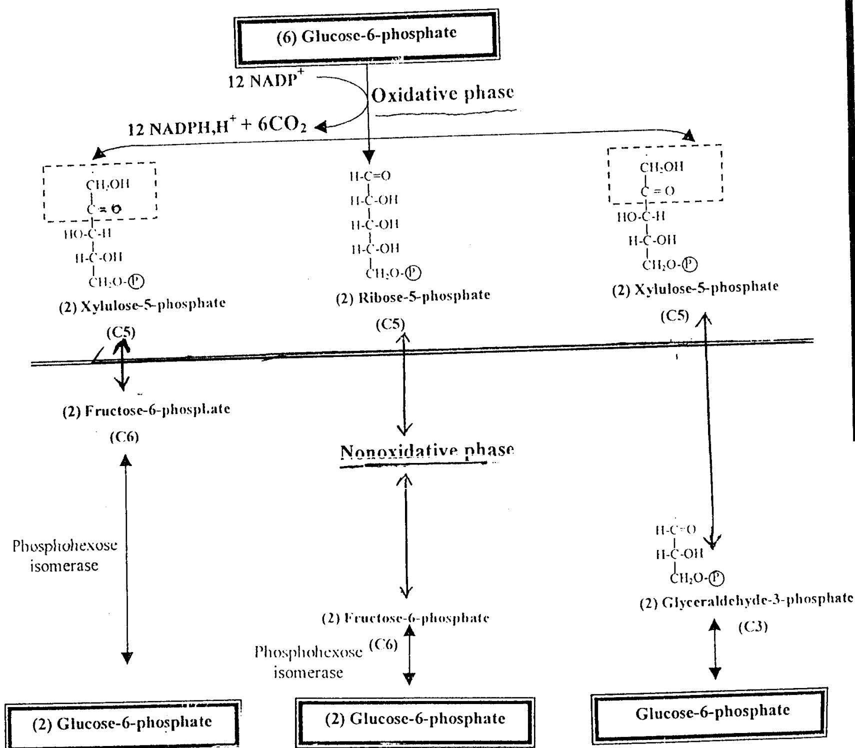
I) Oxidative irreversable phase :

• Glucose – 6 Ph is converted to ribulose – 5 – ph , two moles of reduced $NADP_2H$ and one Co_2 , all above reactions are irreversable.



II) Non oxidative reversable phase:

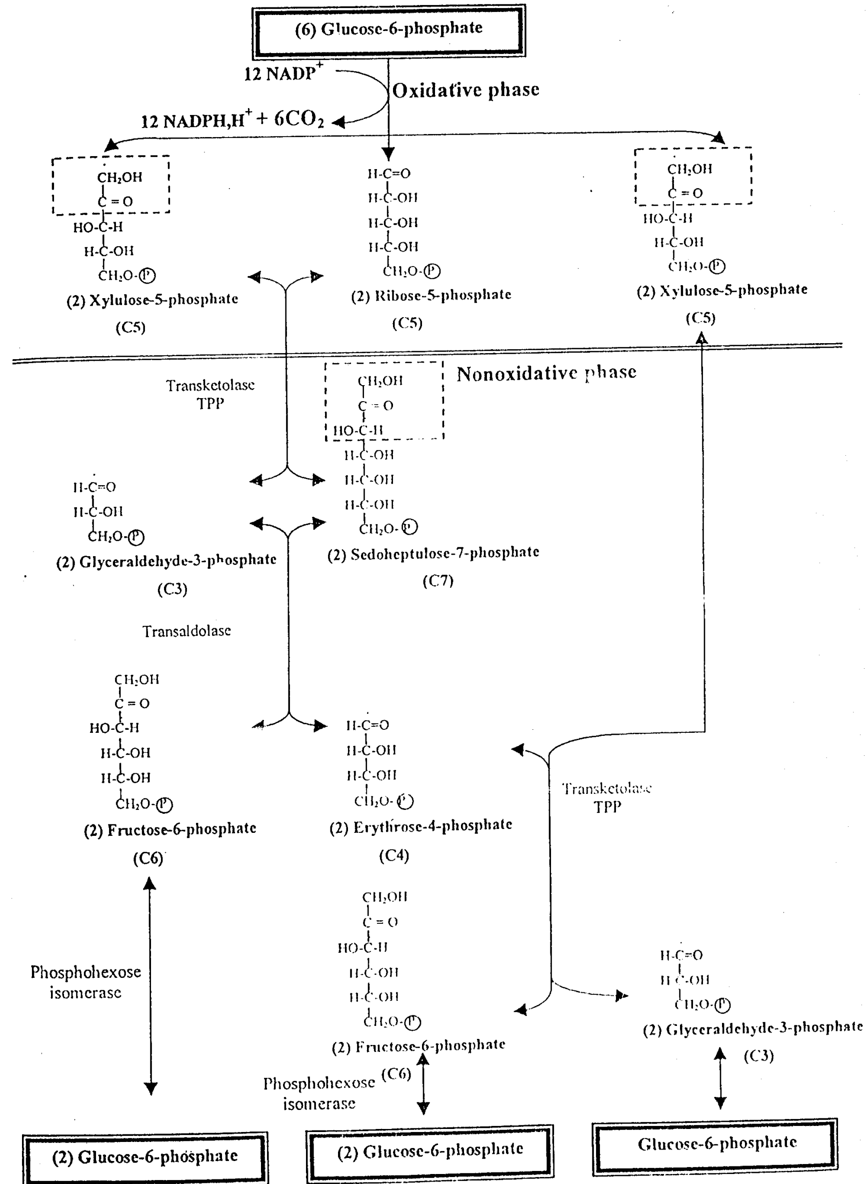
- Six moles of ribulose – 5 – p (30c) are converted back into five molecules of glucose – 6- (30C) , are catalyzed mainly by two enzymes (transketolase and transaldolase) , all reactions are reversable.



Impotence of hexose monophosphate shunt (pathway):

(1) It provides the body with ribose – 5 – ph , which, forms phosphoribosyl pyrophosphate (PRPP) for synthesis of nucleic acids, and nucleotides (FAD, NAD , ATP).

II- Non-oxidative Phase: This phase is reversible. It catalyzes the conversion of 6 molecules of pentoses produced by phase one into 5 molecules of glucose-6-phosphate.

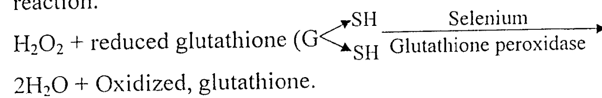


(2) It is the main source of NADPH required for many reactions :-

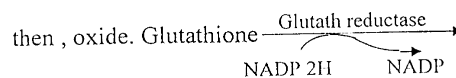
- Synthsris of fatty acids (lipogenesis) , cholesterol, and galactolipids.
- Synthesis of non essential amino acids.

(3) Glutathione reduction by NADPH :

- H_2 O_2 is a powerful oxidant (produced in the body) that results in damage to cellular DNA, phospholipids of cell membrane , and also can oxidizes iron of Hb to form the useless ferric methemoglobin (Fe^{+++}) .
- Reduced glutathione can get red of toxic H_2O_2 through the reaction.



$2H_2O$ + Oxidized, glutathione.



reduced glutathione to act once more.

(4) **importance of HMP in red cells : (favism)**

- Red cells are liable for oxidative damage due to their role in oxygen transport.
- H_2O_2 in red cells oxidizes the iron of Hb to form methemoglobin , also H_2O_2 produces lipid peroxidation of red cell membarane which increases its fragility, so red cells is liable to lysis → hemolytic anemia and jaundice.

- Production of NADP 2H in pentose shunt protects these cells from damage by regeneration of reduced glutathione which destructs the H_2O_2

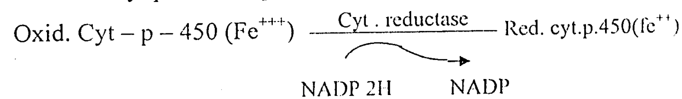
- In favism, there is genetic deficiency of glucose – 6 – ph dehydrogenase → impairment of pentose shunt → decrease reduced $NADP_2H$ → decreased reduced glutathione → increase H_2O_2 → red cell lysis.

- Fava beans contain oxidizing agents as divicine and isouramil → red cell lysis in patients with favism.

- Also certain drugs as permaquine, aspirin, or sulpha stimulate the production of H_2O_2 .

(5) Reduction of oxidized cytochrome – P450 → reduced cyt.p.450 in presence of cyt. reductase and NADP 2H.

- Reduced Cyt.p450 is important in detoxicating processes.

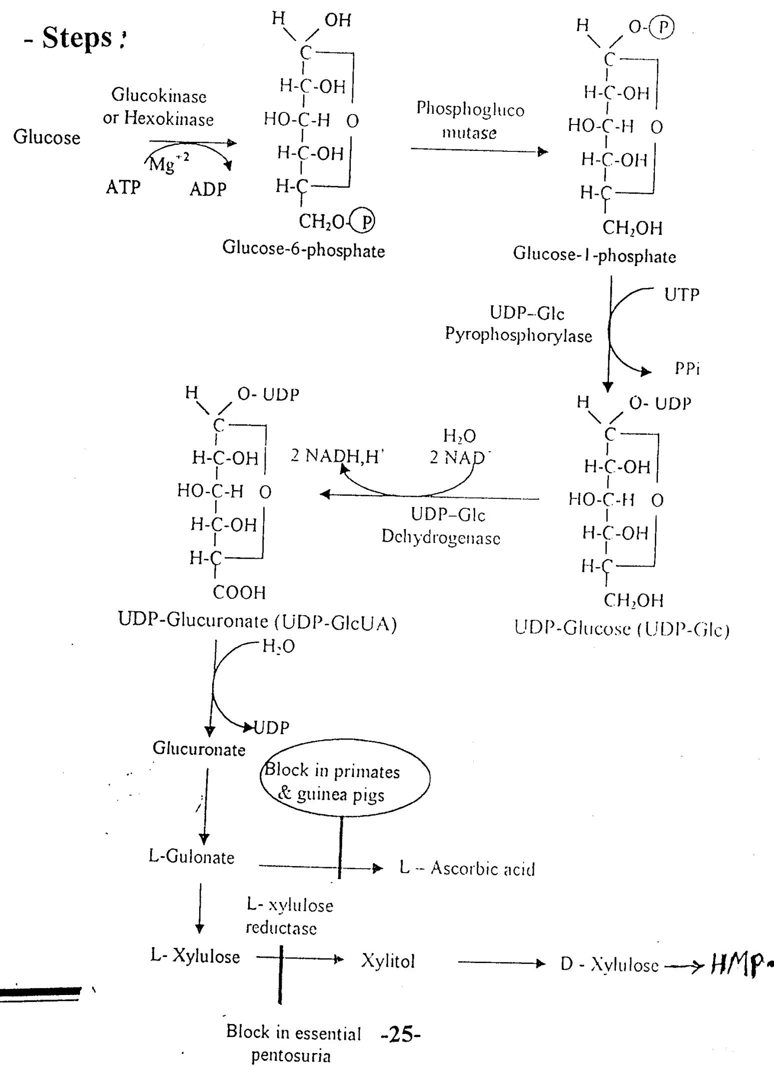


- **Regulation of HMP** : the key enzyme glucose.6. ph. dehydrogenase is stimulated by insulin and oxid NADP , and inhibited by NADPH+ H accumulation.

The Uronic Acid Pathway

- Is alternative oxidation of glucose leading to formation of glucouronic acid , no energy is generated.
- It occures mainly in cytosol of liver cells.

- Steps :



- **Importance :**

The active form of glucouronic acid (UDP – glucuronate) is utilized in many functions:

(1) Synthesis of glycosaminoglycans.

(2) It is used as detoxicating agent by conjugation with toxins to be more soluble and easily excreted (in urine or bile) as steroid hormones, phenols, xenobiotics, and bilirubin → bilirubin – diglucouronide (direct bilirubin)

(3) In many mammals glucouronate is converted to ascorbic acid (VIT.C), but not in humans.

(4) Glucuronic acid may be converted to the pentose L. xylulose.

- **Essential pentosuria :**

It is rare genetic deficiency of L. xylulose reductase → accumulation of L. . xylulose → excreted in urine.

Glycogen Metabolism

- Glycogen is the major carbohydrate store in human, present in liver and muscles.
- It occures mainly in cytoplasm of liver (8 – 10% of its weight, about (100- 120 gm glycogen)
- Liver glycogen maintain blood glucose during fasting for about 12 – 18 hours (keeps blood glucose constant).
- Muscle glycogen (about 1% of its weight ; 350 – 400 gm glycogen) supplies glucose to muscles only during contraction , not to blood due to deficiency of glucose – 6 . phosphatase enzyme.
- Muscle glycogen is depleted only after prolonged exercise.

Glycogen metabolism include the following :

- **Glycogenesis :**
  Formation of glycogen from glucose.
- **Glycogenolysis:**
  Breakdown of glycogen to glucose in liver, and glucose – 6. ph in muscles.
- **Gluconcogenesis :**
  Formation of glucose from non carbohydrate compounds.

Glycogenesis

- Is formation of glycogen in liver and muscles

- Sources :

I) **liver glycogen**

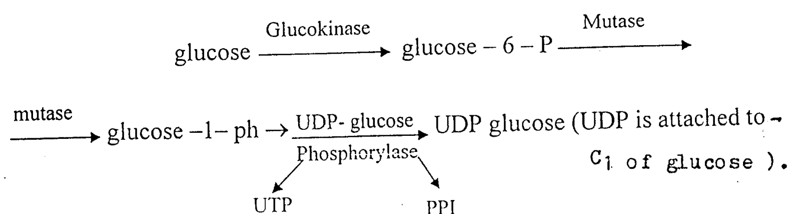
- Blood glucose.
- Other sugars ; as fructose & galactose in liver.
- Non carbohydrate sources : by gluconeogenesis as amino acids , glycerol and lactic acid .

II) **Muscle glycogen :**

- Blood glucose only.

- Steps :

1) glucose molecules must be activated first to active nucleotide glucose (UDP – glucose)

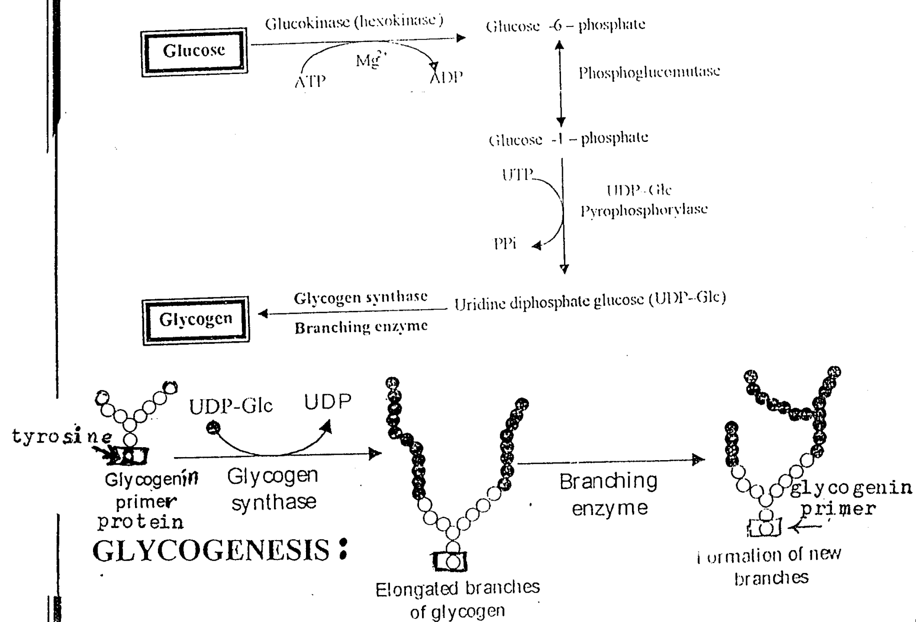


2) The UDP – glucose molecules are added to a glycogen primer (precursor) to form glycogen.

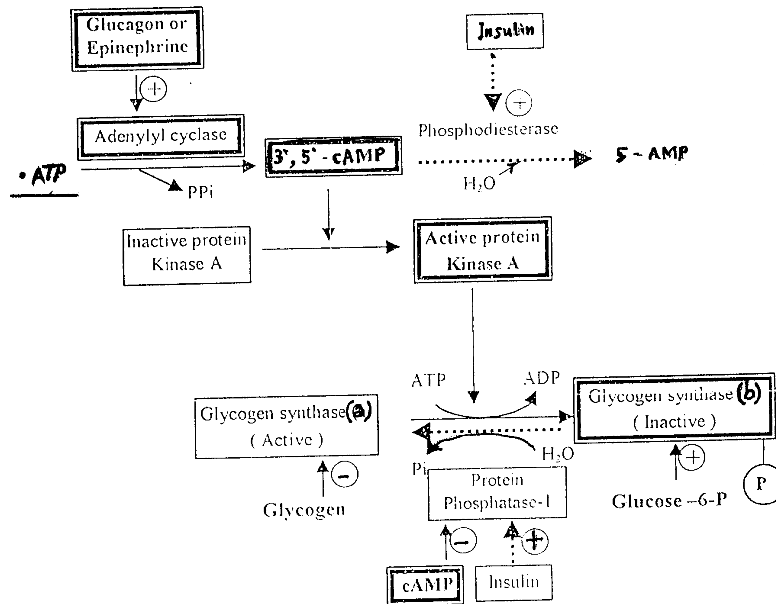
Glycogen primer : (GLYCOGENIN PRIMER)

Glycogenin is a small protein , is glycosylated by active nucleotide – glucose (UDP – glucose) in its tyrosine residue forming the orginal primer , then the UDP – glucose molecules are added to that original primer forming the glycogen primer which is elongated in chains at α1-4 link via the key enzyme glycogen synthase.

- Glycogenin protein + UDP glucose → glycogen primer
- glycogen primer + UDP glucose $\xrightarrow[\text{Synthase}]{\text{Glycoge}}$ 1.4 glycosyl units + UDP
- Branching enzyme : catalyzes the synthesis of glycogen of α 1- 6 link at branches to form the whole glycogen molecule.
- The glycogen primer remains in the center of glycogen molecule.



Regulation of Activity of Glycogen Synthase :



- Regulation of glycogensis :

(i) The active key enzyme is dephosphorylated glycogen synthase (a) form.

(ii) **Insulin :** activates phosphodiesterase which destructs cAMP → inactivation of protein kinase A. → maintaining, and activation of glycogen synthase → activation of glycogenesis in liver, and muscles.

(iii) **Glucagon (in liver) and epinephrine (in muscle and liver):** Hormones Attach to cell membrane receptors → signals → production of the regulatory G. protein (depends upon GDP/ GTP system) → stimulate adenyl cyclase → increase c AMP → stimulate protein kinase. A → inhibit glycogen synthase → inhibition of glycogenesis.

Glycogenolysis

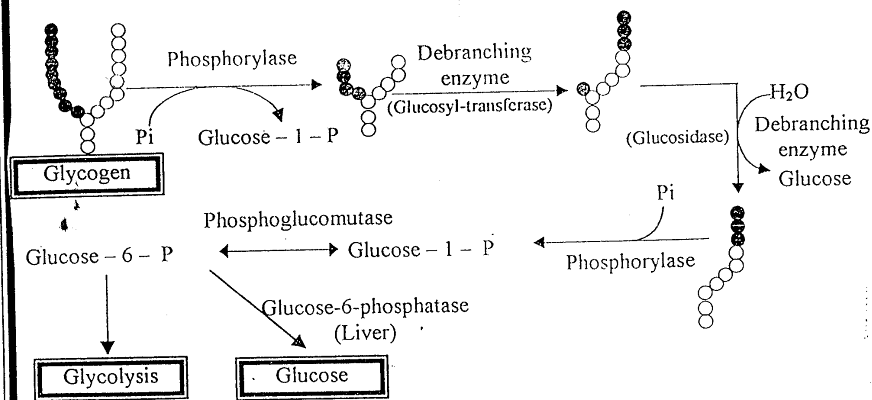
- is breakdown of liver glycogen (during starvation) into blood glucose.
- And muscle glycogen into glucose –6– ph (during muscle exercise) due to deficiency of glucose –6– phosphatase in muscles , then proceede by anerobic oxidation to pyurvate or lactate.

Steps :

(1) The active phosphorylated Glycogen phosphorylase (a) is the key enzyme to remove glucose from α 1-4 glycogen chain , and debranching enzymes to remove glucose at α 1- 6 glycogen branches in the form of glucose – 1 – ph.

- Glucose – 1 – ph is formed , and by glucomutase → glucose. 6 – p.
- Glucose – 6 – ph $\xrightarrow[H_2O\text{(in liver)}]{\text{Glucose – 6 – phosphatase}}$ glucose unit +Pi

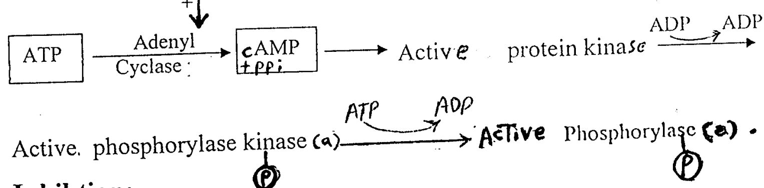
(2) In muscles , no glucose – 6 – phosphtase, thus glucose – 6 – ph undergoes glycolysis to pyruvate or lactate during muscular exercise .



GLYCOGENOLYSIS

Regulation of glycogenolysis:

- Glycogen and thyroxin stimulates glycogenolysis mainly in liver, through stimulation of c AMP.
- Adrenaline & nor odrenaline stimulates glycogenolysis mainly in muscles, also in liver , though stimulation of c AMP.



Active. phosphorylase kinase (a) —ATP→ADP→ Active Phosphorylase (a).

Inhibtion:

insulin ingibits glycogenysis throught destruction of c AMP.

N.B:

c AMP promotes glycogenysis and lipoltysis.

Glycogen Storage Diseases

Are inhireted disordes leaders leading to deposition of glycogen in tissues , special liver and kidney.

Causes:

- Deficiency of enzymes invloved in glycogenolysis , such as : glucose – 6 – I phosphatase, depranaching enzymes, may phosporlyrlase in muscles.

Types:

Type I : Von Gierke's disease : the commonest type

* There is dificincy of glucoe -6- phosphatase in liver and kidney → accumulation of glucose -6 ph- and glycogen.

- Liver is enlarged with glycogen → disordess In liver function.

* Fasting hypoglycemia.

Hypenlipdemia and retosis due to acclerated falty acid oxidatron to liberate energy.

* Accumulation of qlucose -6-ph → stimulates pentose shunt → increases PRPP (first step in purine synthesis) → increases uric acid → gout.

Type II : Pompe's disease

* Glycogen accumulates in lysosomes due to deficiency of glycosidase (acid mattase).

Type III : Limt dextrinosis = Cori,s disease

* Accumulation of short branches in liver & muscles due to deficoency of debranching enzymes.

Type IV : Amglopectinosis

* There is deposition of few branches glycogen due to deficiency of branching enzymes.

Type V : Mc-ARDce's disease

* There is deficiency of phoshory case in muscles → muscle cramps during exercise, and increase CDR, LDH
* High glycogen coirtent (2.5 – 4.7)

Type VI: (hers' diseare)**:** Due to deficiency of (liver phosphory base)

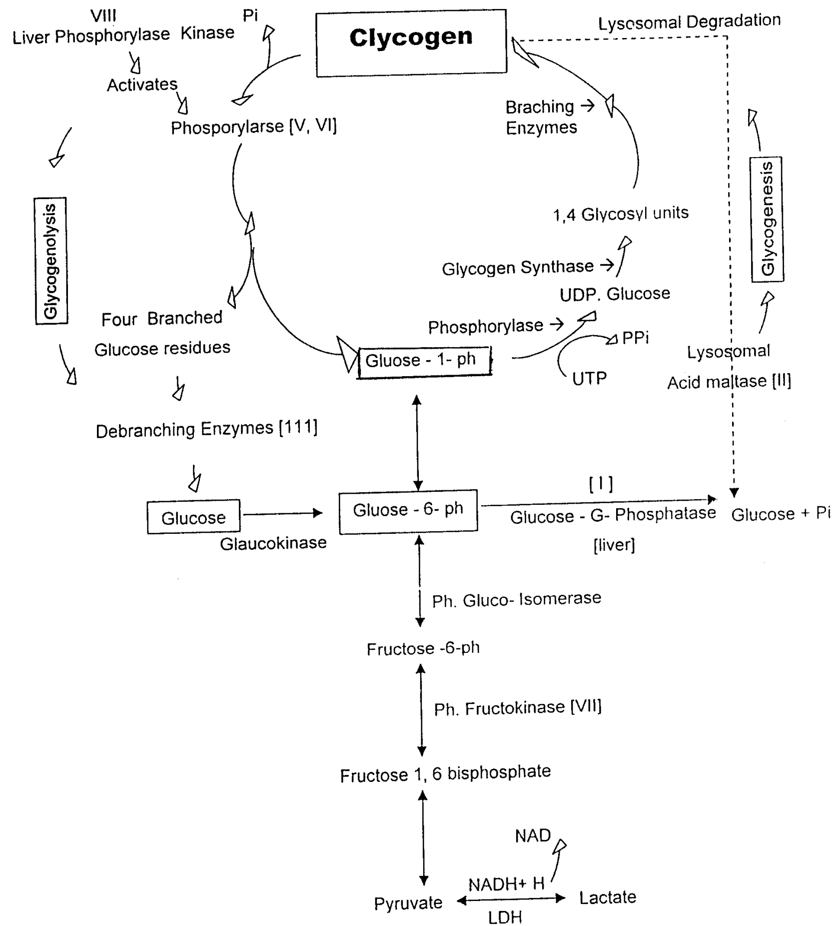
* High liver glycogen, hypolycemia.

Type VII (Tarui's disease) and red cells :

Due to deficiency of ph : (Fructokin in museles)

* Picture as in type V, but also may hemolytic anemia.

Carbohydrates Metabolism



Pathway of Glycogen metabolism

Associated with glycogen storage disease types [I → VIII]

Gluconeogenesis

It is formation of glucose or glycogen from non carbohydrate origins to supply blood glucose is cases of fasting, starvation, and low carbohydrate diet , and after depletion of liver glycogen.

Glucogenic non carbohydrate substances:

Glucogenic amino acids , glycerol , lactic acids , pyruvates, ...

- Site :

It accuses mainly in liver , and kidney (has its enzymes).

- Gluconeogenic Key enzymes:

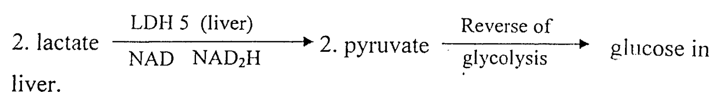
1. Glucose – 6 – phosphatase (not present in skeletal muscles and adipose tissue).
2. Fructose 1, 6 bisphosphatase (is abscent from heart , and smooth muscles).
3. Pyruvate carboxylase in mitochondria (abscent from red cells).
4. Phosphoenol – pyruvate . carboxykinase.

So , Glucongeonesis does not occure in skeletal muscle , heart and adipose tissue.

- Steps:

All gluconogenic substances are converted to pyruvate then to glucose ; or the reverse of glycolysis , such as :-

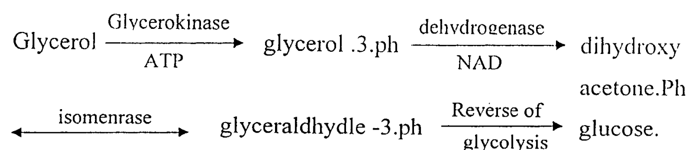
A) lactate : in muscles & RBcs



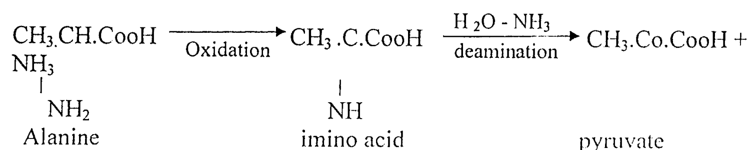
liver.

as it occures in Cori cycle .

B) Glycerol : from lipolysis :



C) Glycogenic amino acids : (through deamination or transamination)



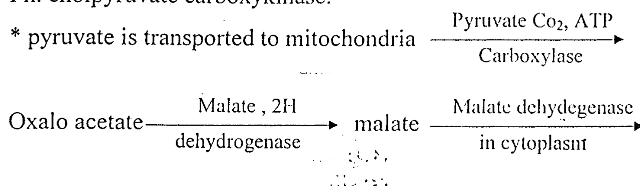
* As it accures in glucose alanine cycle : alanine in muscles is converted to glucose in liver.

- **Pyruvate → glucose pathway is proceeding (reversible) except three irriversable reactions which can be overcomed:-**

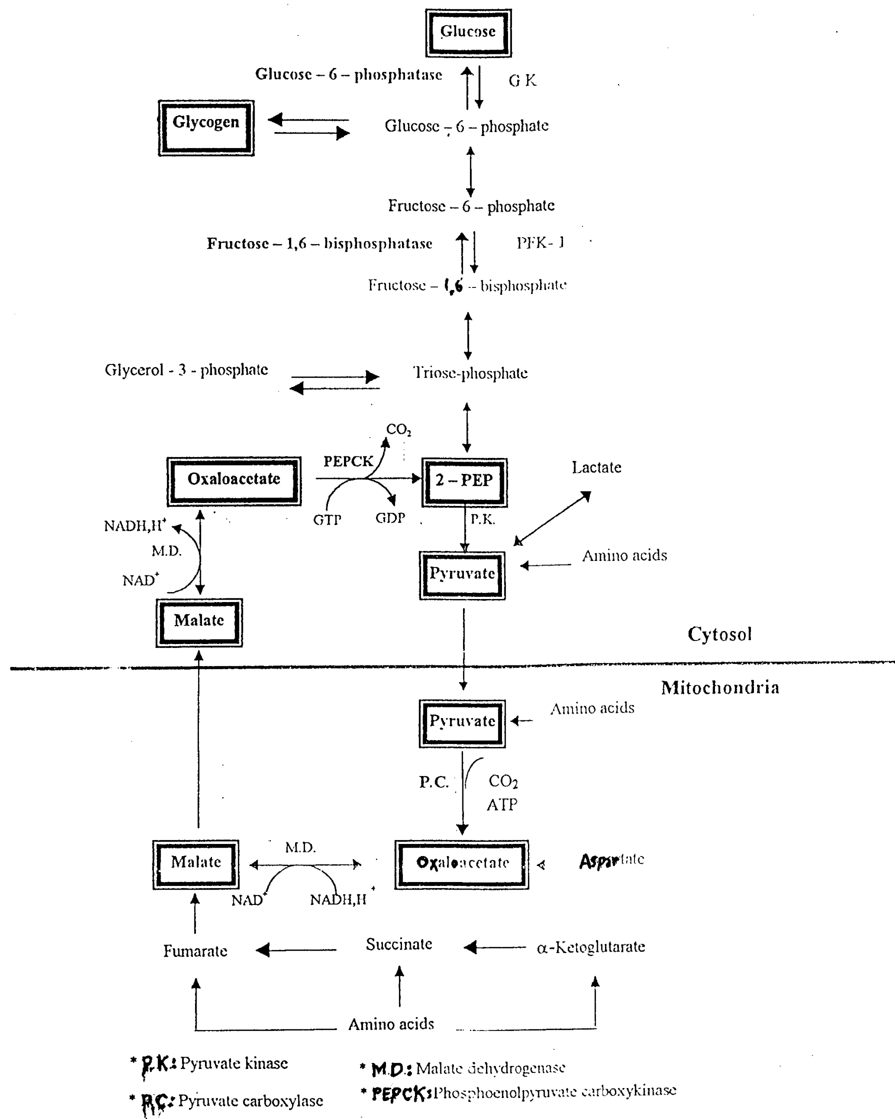
(1) **[Pyruvate → ph. Enol.pyruvate]** this can be overcomed by two enzymes :

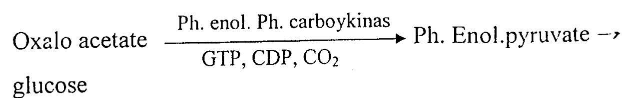
i) pyruvate carboxylase

ii) Ph. enolpyruvate carboxykinase.



Summary Diagram for Gluconeogenesis





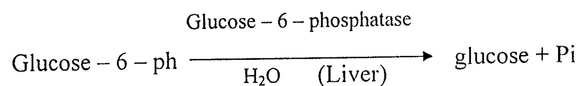
glucose

II) [Fructose 1, 6 bisphosphate → fructose – 6. ph]

* Fructose 1,6 bisphosphate is converted back to fructose – 6. ph by the key enzyme fructose 1,6 bisphosphatase in the liver.

III) [Glucose – 6 – ph → Glucose]

Glucose – 6. phosphate is converted back to glucose by glucose 6. phosphatase in liver.



- Factors affecting gluconeogenesis :-

- Stimulation :

Gluco.corticoids , Glucagon , epinephrine , and growth hormones induce key enzymes synthesis of gluconeogenesis .

* **Gluco.corticoids :-** Inhibit glucose oxidation to save blood glucose , also stimulate protein catabolism → increase glucogenic amino acids.

- inhibition :

insulin inhibits key enzymes synthesis of gluconeogenesis , and stimulates glycolytic enzymes.

Pi
Glucose
ATP
Glucose-6 phosphatase
Glucokinase
H_2O
Glucose 6-P
ADP

Pi
Fructose-6-P
ATP
Fructose 1,6-diphosphatase
Phosphofructokinase
H_2O
Fructose 1,6-diphosphate
ADP

Glyceraldehyde-3-P
Dihydroxyacetone-P
NAD^+
Glycerol-3-phosphate dehydrogenase
1,3-diphosphoglyceric acid
$NADH+H^+$
3-phosphoglyceric acid
Glycerol-3-P
ADP
Glycerolkinase
2-phosphoglyceric acid
ATP
Glycerol

Phosphoenol pyruvate
ADP
Pyruvate kinase
ATP
$GDP + CO_2$
Phosphoenol pyruvate carboxykinase
GTP
Pyruvate
Lactate

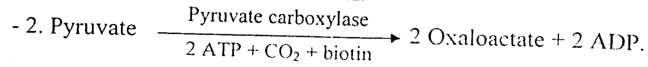
Oxaloacetate
$NADH + H^+$
Malate dehydrogenase
NAD^+
Malate

Pyruvate
ATP
CO_2
Pyruvate carboxykinase
ADP+Pi
$NADH + H^+$
Oxaloacetate
Acetyl-CoA
NAD^+
Malate
Citrate
Fumarate
α-Ketoglutarate
Succinyl-CoA
Propionate
MITOCHONDRIA
CYTOSOL

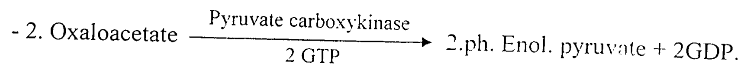
: MAJOR PATHWAY OF GLUCONEOGENESIS IN THE LIVER. ENTRY POINTS OF GLUCOGENIC AMINO ACIDS ARE SHOWN BY ARROWS

- Energy Utilization for gluconeogenesis :

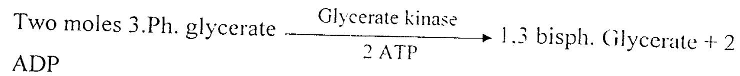
for conversion of two moles of pyruvate → one mole glucose , 6 moles of ATP are utilized, also two NAD2H.

- 2. Pyruvate


2 Oxaloactate + 2 ADP.

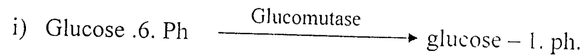
- 2. Oxaloacetate


2.ph. Enol. pyruvate + 2GDP.

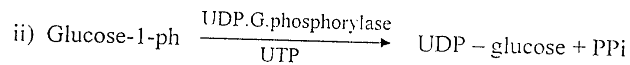
Two moles 3.Ph. glycerate


1.3 bisph. Glycerate + 2 ADP

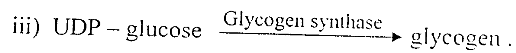
* **If converted into glycogen, extra one ATP is utilized :**

i) Glucose .6. Ph


glucose – 1. ph.

ii) Glucose-1-ph


UDP – glucose + PPi

iii) UDP – glucose


glycogen .

- Importance of gluconeogenesis :

(1) maintenance of blood glucose :

a) During fasting brain needs (120 gm.glucose /day) , in addition to other body needs (190 gm /day) , but all body fluids contains not more than 25 gm , so in starvation (after depletion of liver glycogen) other source is required as gluconeogenesis for brain (nervous system) and red cells , so failure of gluconeogenesis is usually fatal.

b) Gluconeogenesis supplies body cells with glucose 4–6 hours after the last meal, and reaches its peak after depletion of liver glycogen.

(2) in brain

* Glucose is the main source of energy to brain tissues .
* In low carbohydrate diet , starvation , stress or severe exercise , brain can not utilize fatty acids , but can utilizes ketone bodies after 5 -6 days , so gluconeogenesis is essential otherwise hypoglycemia causes brain dysfunction, convulsions → Coma → death.

d) In red cells:

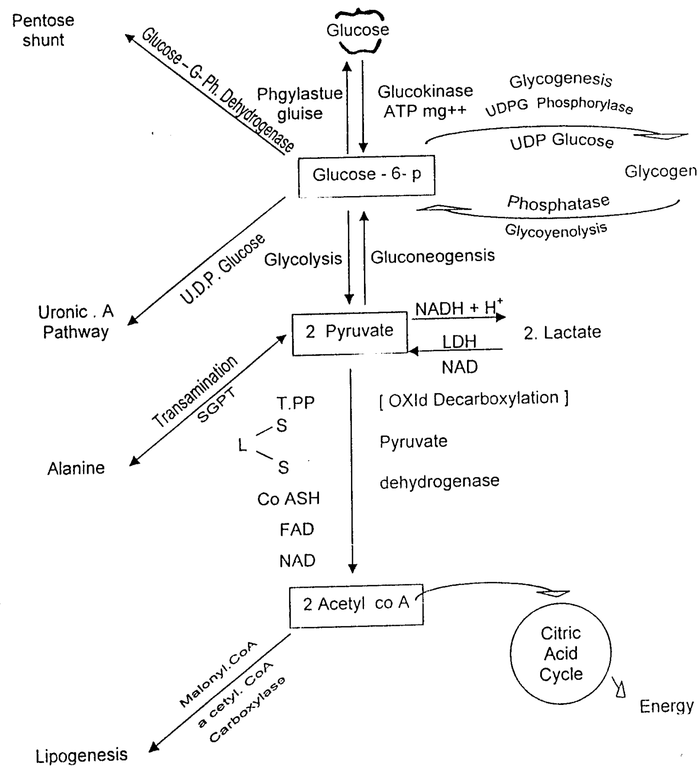
Glucose is the only source of energy in red cells.

e) **Skeletal muscles** :

depend upon glucose only under anerobic conditions (exercise).

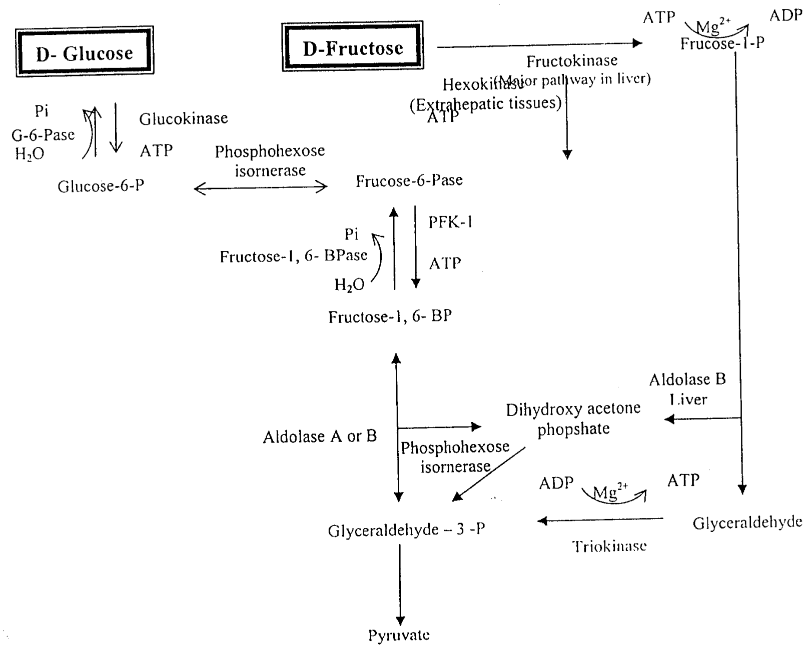
2) Gluconeogenesis clarifies circulation from body metabolites as lactate produced by red cells , and contracting muscles , also glycerol produced by lipolysis in adipose tissues.

3) Gluconeogenesis is essential for nutrition of fetus, and synthesis of lactose in mammary gland.



General Scheme of Carbohydrate Metabolism

METABOLISM OF OTHER SUGARS
FRUCTOSE METABOLISM

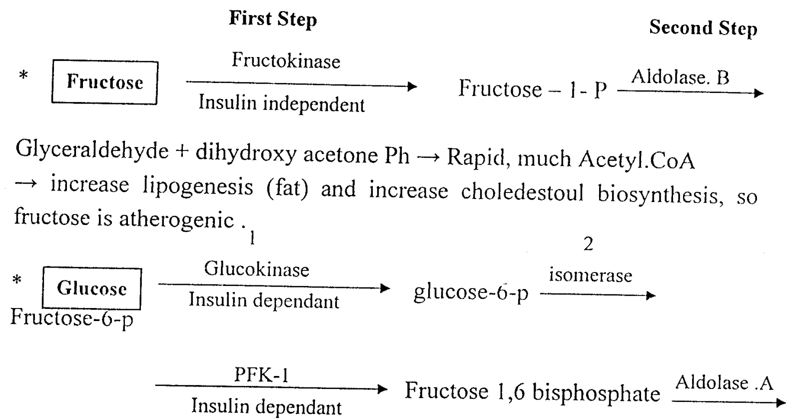


Utilization of Fructose

1- In Liver:

Fructose is converted to glucose. It is metabolized mainly in the liver by the fructokinase enzyme to form F-1-P. Then by the action of fructose-1-phosphate aldolase (aldolase B), F-1- P is converted to DHAP and glyceraldehyde. The latter is converted to glyceraldehyde-3-phosphate by the triokinase. DHAP and glyceraldehyde-3-phosphate form glucose by reversal of glycolysis or converted to pyruvate.

The utilization of fructose by fructokinase then aldolase B, bypass the steps of glucokinase and PFK_1 which are activated by insulin. This explains why fructose disappears from blood more rapidly than glucose in diabetic subjects.



Glyceraldehyde + dihydroxy acetone Ph → Rapid, much Acetyl.CoA → increase lipogenesis (fat) and increase choledestoul biosynthesis, so fructose is atherogenic .

* Glucose —(1) Glucokinase / Insulin dependant→ glucose-6-p —(2) isomerase→ Fructose-6-p

—PFK-1 / Insulin dependant→ Fructose 1,6 bisphosphate —Aldolase .A→

Glycesraldhyde-3-p + dihydroxyacetone –ph

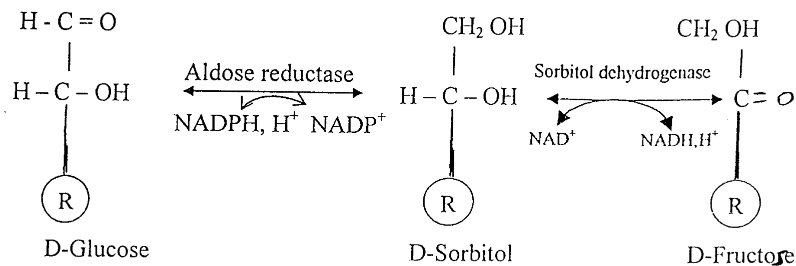
* So, glucose needs four step to reach glyceroldhye-3-p and is insulin dependant.

But fructose needs two steps only and is insulin independent.

2- In Extrahepatic Tissues:

Fructose is converted to F-6-P by the hexokinase. However, the hexokinase has a very low affinity for fructose compared to glucose. So, it is not a significant pathway for fructose metabolism, unless it is present in very high concentration in blood.

Synthesis of Free Fructose



By this mechanism glucose is converted to fructose in seminal vesicles and secreted in seminal fluid. Also, conversion of glucose to sorbitol is increased in diabetic subjects, sorbitol produces osmotic damage of cells, which may account for production of diabetic cataract, retinopathy, nephropathy and neuropathy.

Hereditary Defects in Fructose Metabolism

These metabolic inborn errors include mainly:

1- Essential Fructosuria

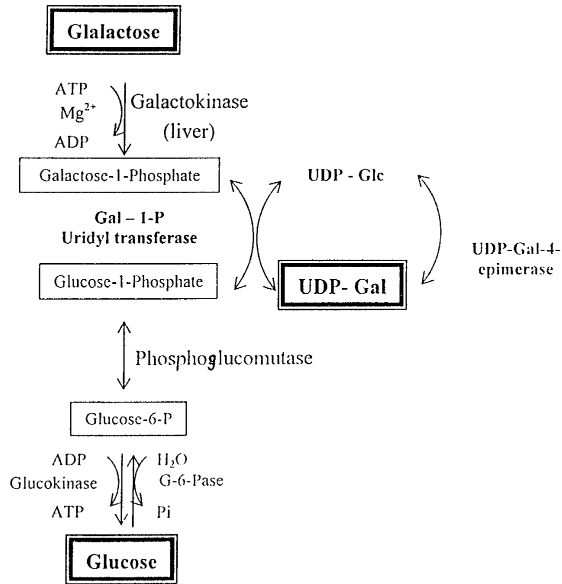
It is due to hereditary deficiency of the **fructokinase enzyme** and manifested by fructosemia and fructosuria.

2- Hereditary Fructose Intolerance

It is due to hereditary deficiency of the liver enzyme **aldolase B.** This leads to accumulation of fructose -1- phosphate and depletion of liver phosphate, which produces inhibition of glycogen phosphorylase and **hypoglycemia** after fructose feeding.

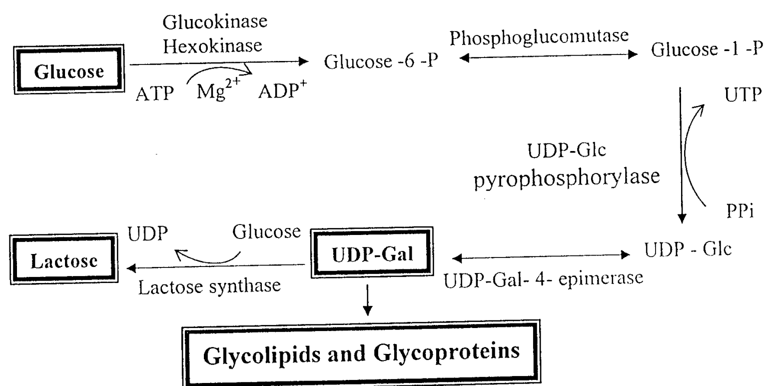
GALACTOSE METABOLISM

Utilization in liver



The conversion of galactose to glucose in the liver (as shown in the diagram), starts by the **galactokinase,** which forms galaetose - 1 - phosphate. The latter is converted to UDP galactose by the enzyme **galactose-1-phosphate uridyl transferase UDP** galactose from UDP- Glc by the enzyme **UDP galactose- 4 - epimerase** and the cycle is repeated.

Synthesis of Lactose and Galactose Containing Compounds

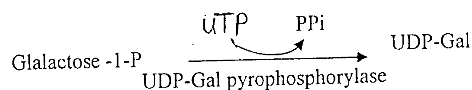


Galactosemia

This is inability to metabolize galactose causing **galactosemia** (elevated blood levels of galactose) and **galactosuria** (presence of abnormal amounts of gal actose in urine). Galactosemia may be caused by inherited defects in galactokinase, **uridyl transferase** or 4-epimerasc. The most common is deficiency of the uridyl transferase. Galactose increases in blood and it is reduced in the eye by aldose reductase to form **galactitol** (dulcitol), which accumulates causing **cataract.** Also accumulation of galactose -1-phosphate and depletion of liver phosphate inhibit glycogen phosphorylase, which result in hypoglycemia after galactose or lactose feeding. Later on, **liver failure, mental deterioration and neurological dysfunction** are common **complications.** These complications can be avoided by giving a **galactose free diet.**

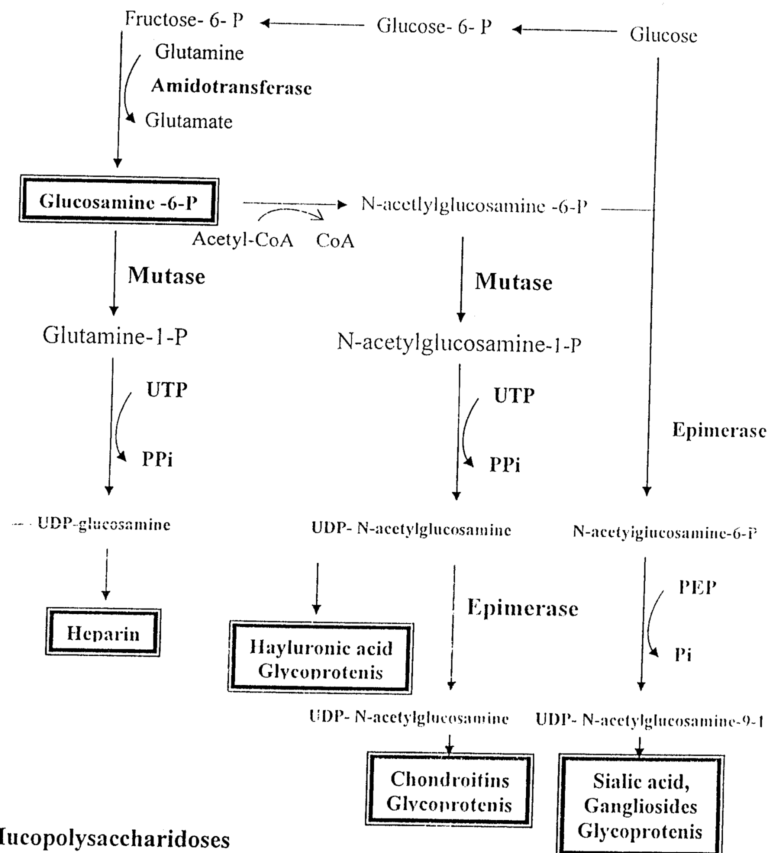
Children are able to form UDP-GaL from UDP Glc by the epimerase, which explain their normal growth and development.

Later on, children who have uridyl transferase deficiency can utilize **galactose normally due** to the development of the enzyme **UDP-galactose pyrophosphorylase** which can replace the galactose-1-phosphate uridyl-transferase.



METABOLISM OF AMINOSUGARS

Aminosugars and their derivatives are important constituents of glycosaminoglycans (GAGs or mucopolysaccharides), glycoproteins and glycolipids. They are formed from glucose as follows: -



Mucopolysaccharidoses

These are a group of inborn errors of metabolism due to genetic deficiency of one of the lysosomal enzymes that degrade GAGs, leading to their accumulation in tissues. Patients are presented by, cloudy corneas, mental retardation, stiff joints and hepatospleenomegaly. The disease is usually progressive and leads to early death in childhood.

Blood Glucose

- **Normal Values :**

  - Fasting level (8-12 hours fasting): 65- 110 mg%.
  - Two hours post prandial up to 140 mg%.
  - Neonatal born : 40 – 60 mg%.
  - Premature infant : below 40mg%.

- **Hyperglycemia:**
  Fasting level above 14 mg%.
- **Hypoglycemia :**
  Below 65 mg%.
- **Hypoglycemic Coma :**
  Below 40 mg%.

Sources of blood glucose:

(1) **Carbohydrates of diet:**
Starch sucrose, lactose, glucose and fructose ; all are converted to glucose in the liver.

(2) **Glycogenolysis:**
In first 12- 18 hours fasting in liver.

(3) **Gluconeogensis:**
As lactate, glycerol, glycogenic amino acids all are converted to glucose in liver after depletion of liver glycogen.

Regulation of blood glucose
(glucose homeostasis)

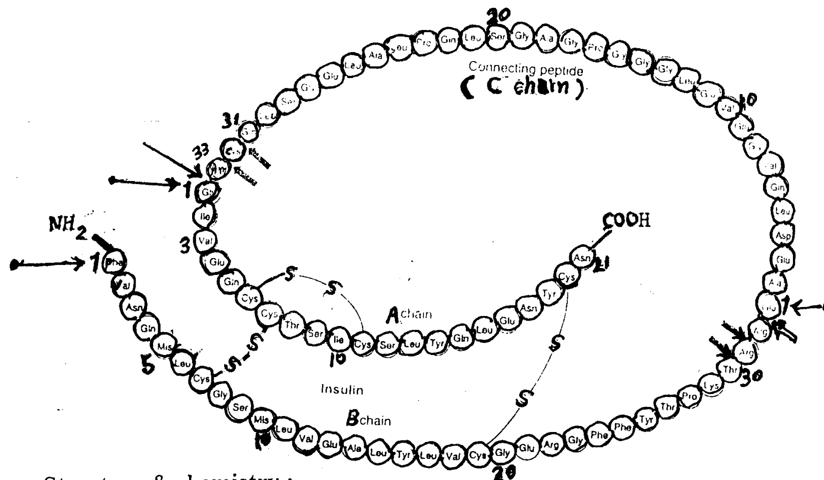
Blood glucose remains stable within its normal range in spite of fasting (hypoglycemic condition) or over carbohydrate feeding (hyperglycemic condition), due to the following factors:

I) Hormonal (endocrinal) regulation :-

A) In Hyperglycemic condition by :

- Insulin : (51 amino acids)

- pancreas contains the langerhans cells which form 1-2% of its weight and consist of 25% alpha cells → glucagon, 70% beta cells → insulin, and 5% delta cells → somatostation.



- Structure & chemistry :-

Insulin is secreted in inactive form (proinsulin) in granules containing zinc in the ribosome of B- cell of pancreas (its gene is locted in chromosome 11).

- The proinsulin peptide structure is arranged in three peptide chains : A chain (21 AA), B (30A .A) and C chain (33A .A).
- Chains A , B are connected together by two strong disulphide bonds , through its cystiene residues.
- Proinsulin diffuses into the golgi apparatus of B cells, where the peptide C chain is separated leaving the active insulin (A & B Chains) containing zinc which is essential to its activity.

- Insulin Secretion :-

- Fourty to fivety units are secreted per day ; equal to one fiveth (1/5) of insulin store (250 units)

- Animal insulin has no C peptide chain, so in cases of hyperinsulinemia (hypoglycemic state), the C Fraction determines the cause of hyperinsulinemia ; if C fraction is deficient → administrated animal insulin.

- But if C fraction is increased → human origin , may parcreatic tumour.

- Diet glucose increases blood insulin within 0.5 minute, maximum insulin is reached when plasma glucose level is at 300 – 500 mg %.

- Some vital organs don't depend upon insulin for glucose uptake, such as : brain , liver , Red cell, and intestine.

- Insulin secretion is inhibited by epinephrine (stress) to spare blood glucose.

- Insulin degradation :-

Occures in liver by insulin glutathione – trans hydrogenase enzyme, mainly by stimulation of thyroxine, the enzyme provides two hydrogens to the disulfide bond leading to separation of A & B chains , then subjected to proteolysis.

- Half life time of plasma insulin is less than 5 minutes.

- Functions of insulin :-

a- **Carbohydrates** :- Insulin decreases blood glucose by:

1) It facilitates entery of glucose to body cells (increases permeability to glucose) specially muscles and dispose tissues (for glycogenesis and lipogenesis respectively).
2) insulin binding to its glycoprotein receptor on the cell evokes signals for glucose transport via glucose transport system present inside the cell to be phosphorylated and oxidized. Mammalian cell may contain up to 20.000 insulin receptors ; with half life time 7 – 12 hours, they ore constantly synthesized and degraded .
3) It stimulates glucokinase to form the active glucose – 6 – ph.
4) It increases glucose oxidation in all body cells.
5) It stimulates glycogenesis via stimulation of glycogen synthase due to destruction of cAMP.
6) It inhibits glycogenolysis (inhibition of phosphorylase), also inhibition of gluconeogenesis by decreasing its enzymes induction.
7) So, by effect of insulin, glucose is converted to energy (50%), or to fat (30-40%) or to glycogen (10%).

b- **Lipids:**

1) it stimulates lipogenesis due to stimulation of its key enzyme (acetyl. co A carboxylase) , also due to inhibition of c AMP.
2) Insulin induces synthesis of plasma lipoprotein lipase → enhances removal of chylomicrones & VLDL from plasma.
3) It inhibits lipolysis by inactivation of hormone sensitive lipase in adipose tissue → decrease circulating free fatty acids, also decrease ketogenesis in liver.

c) **Protein**

insulin stimulates protein biosynthesis by increase synthesis of m RNA,. and increase uptake of amino acids bits tissues (anabolic effect).

B) Hormonal regulation in hypoglycemic conditions:

(1) **Glucagon : (29 A.A)**

- It is secreted from alpha cells of pancrease.
- It stimulates glycogenolysis (especially in liver), through stimulation of c AMP → increase blood glucose.
- Glucagon stimulates gluconeogenoses by induction of its enzymes in liver and kidney.

(2) **Epinephrine & nor epinephrine:**

- They are secreted from suprarenal medulla.
- They stimulate glycogenolysis in muscles and liver , specially during stress , through stimulation of c AMP.
- Inhibit insulin secretion from B. cells to spare blood glucose in stress.

(3) **Glucocorticoids :**

- Secreted from suprarenal cortex.

- Stimulate gluconeogenesis in liver and kidney by induction of its enzymes → increase blood glucose.
- Inhibition of glucose uptake by tissues (muscles and fat cells) → increase blood glucose.

(4) **Thyroxine:**

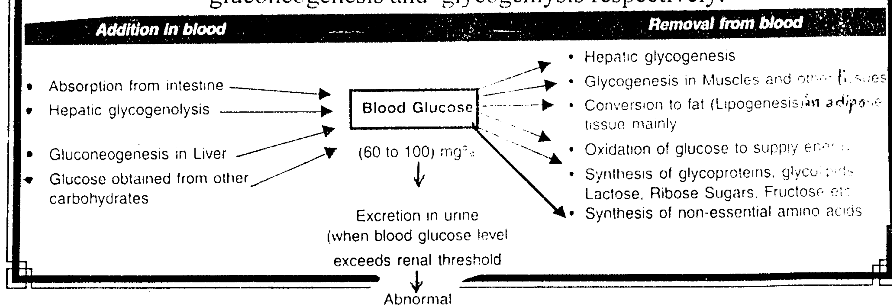
- It is secreted from thyroid as T_3 and T_4 .
- It increases glucose absorption from intestine.
- It stimulates glycogenolysis.
- It increases insulin degradation in liver.
- It has diabetogenic action ; fasting blood glucose is elevated in hyperthyroidism.

(5) **Anterior pituitary hormones :**

i) Growth hormone:-

- It decreases glucose uptake by tissues or muscles.
- It decreases insulin action to all cell membranes.
- Growth hormone secretion is stimulated by hypoglycemia, its maximum secretion is at night, so sweets before bed time is not indicated in children.

ii) ACTH and TSH increase blood glucose by gluconeogenesis and glycogenlysis respectively.



II) Hepatic regulation

(1) During fasting :-

- Liver increases blood glucose by glycogenolysis in first 12-18 hours, and by gluconeogeuesis after depletion of liver glycogen .

(2) after carbohydrate meal :-

- liver increases uptake of blood glucose by glycogenesis, or lipogensis if there is excess of carbohydrates intake.

III) Renal role :

- In normal conditions, blood glucose is filtered and reabsorbed by renal tubules as blood glucose level is below 180 mg% (the renal threshold).
- In hyperglycemia (above 180 mg%) glucose passes the renal threshold → glucosuria, so excess glucose is filtered through the urine.
- Low renal threshold (diabetes innocence):-
  Its value is about 120 mg% , above it → glucosuria.
- High renal threshold :
  Its value is about 220 mg%., above it → glucosuria.

- Somatostatin hormone :-

- Is peptide hormone (14 amino acids) secreted by delta (D) cells of pancreas.
- Is first isolated from hypothalamus, that inhibits growth hormone secretion.
- In pancreas it inhibits glucagon release especially in cases of insulinopenia.

Abnormalites of blood glucose levels

- These may be in the form of hyperglycemia (or diabetes mellitus) and hypoglycemia.

I – Hypoglycemia

- Is drop of blood glucose below normal level (below 65 mg%) , if not treated may proceed to hypoglycemic coma due to brain affection.

- Causes of hypoglycemia:-

i) Postprandial (reactive) hypoglycemia.

- Is temporary drop of blood glucose, about 2-5 hours after carbohydrates meal due to stimulation of insulin secretion.

ii) Fasting hypoglycemia : due to

- **Hyperinsulinism:**
  Tumours of B cells of pancrease or over dose of insulin which may lead to hypoglycemic coma (strong rapid pulse and sweating) especially if there is missed meal.
- **Hyposecretion of anti- insulin hormones :** as glucagon, adrenalin, glucocorticoids (as in addison's disease) and hypothyrodism.
- **liver diseases :** due to decreased glycogen store and impaired gluconeogenesis.
- Chronic renal diseases : leads to impaired gluconeogeuesis.
- Hereditary metabolic disorders : as von Gierk disease.

Effect of hypoglycemia :

Is dangerous because glucose is the main feul of brain, hypoglycemia causes confusion , dizziness , tachycardia, sweating , tremours , may coma and death.

II – Diabetes Mellitus
[Hyperglycemia]

Is state of chronic hyperglycemia with glucosuria due to metabolic disorders of insulin effectiveness as.

i) Inadequate insulin secretion .
ii) Abnormal insulin receptors .
iii) Increase secretion of anti – insulin hormones.

Types :

- **Type I ; insulin dependent diabetes:- (10 – 20%).**
  - There is absolute deficiency of insulin, it may be genetic or due to viral infection in (mumps).
  - It affects youny ages , below 20 years age.
  - It depends upon insulin as management, ketosis may develop.
  - About 80% has insulin antibodies to B islet cells.

- **Type II, insulin independent diabetes :(80- 90%).**
  - There is resistance to insulin action at cell receptors (there is up to 20.000 per/cell).
  - It affects old ages, above 40 years age.
  - It is managed by oral hypoglycemic drugs.
  - Insulin may be increased (hyperinsulinism , and may obesity).

Biochemical disturbances of diabetes mellitus

I) Carbohydrate disorders:

- Glucose transport decreases in diabetes → Hyperglycemia → glucosuria → polyurea → dehydration (dry mucus membranes).
- Dehydration with hyperglycemia → hyperosmosis → dehydration of brain cells → Coma.
- Polyurea leads also to loss of water souble vitamins (B1,6) → peripheral neuritis. And decreased intracellular glucose leads to polyphageia, and decreased amounts of ATP→ easily fatigue.
- Polyurea leads also to loss of electrolytes as K^+& Na^+.
- Glucosuria occures, if blood glucose exceeds 180mg%.

II) (Lipid disorders):

- Decreased lipogenesis and increased lipolysis in adipose tissues → loss weight and increase fatty acids.
- Fatty liver due to over mobilization of depot fat to liver.
- Increase oxidation of fatty acids → hypercholesterolemia and ketonemia → may fatal ketoacidosis.
- Hyperlipidemia due to decrease clearance of VLDL by lipoprotein lipase [insulin stimulate synthesis of the enzyme).

III) Protein disorders

- Decrease protein synthesis and increased protein breakdown → muscle wasting.

- Decrease antibody formation , delayed wound healing.
- Increase non protein nitrogen in urine (urea and creatinine) due to excessive protein catabolism.

IV) Water & electrolytes disorders:

- Polyuria, polydepsia and dehydration.
- loss electrolytes as Na^+ and K^+ (may hypokalemia).
- Proteinuria if there is kidney damage.
- Insulin aids transfer of K^+ into cells, so in management Kcl should be supplied to prevent hypokalemia:

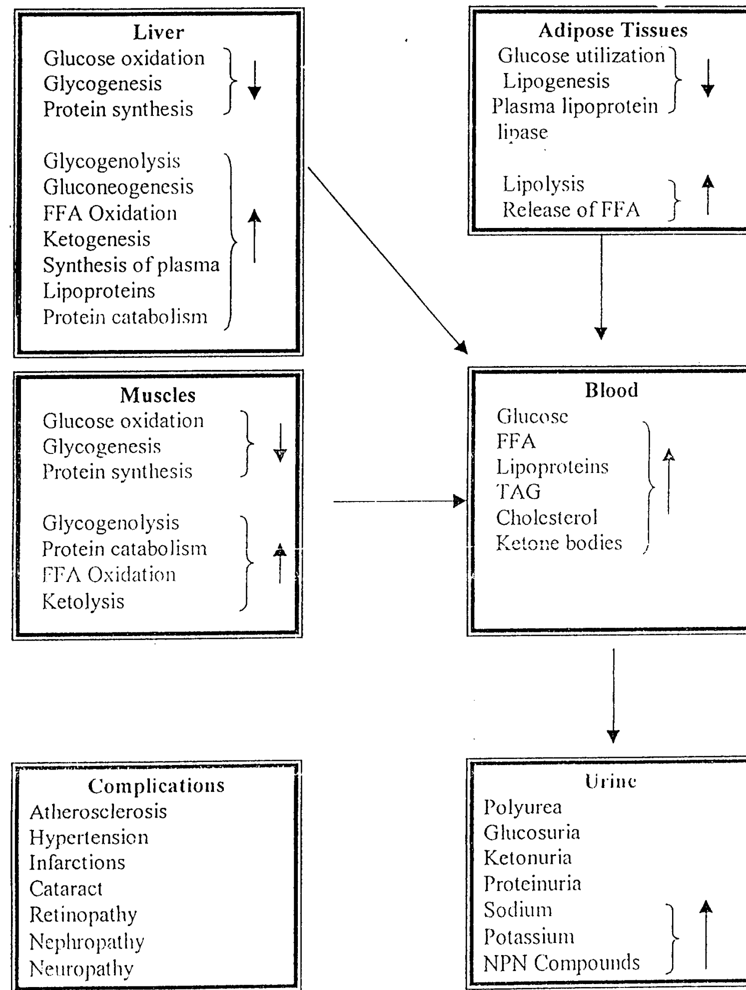
-damage to vascular system → initiates atherosclerosis, hypertension , kidney failure and myocardial and myocardial infraction.

V) Diabetic cataract due to sorbitol accumulation, also diabetic retinopathy , nephropathy , and neuropathy due to vascular damage.

VI) Vascular complication :

- Hyperglycemia → formation of glycosylated proteins aggregates → damage to vascular system → initiate athero-sclerorsis, hypertension, kidney failure and myocardial infraction.

Summary of Important Changes in DM



Lab. Diagnosis and follow up of diabetes mellitus

I – Urine

a) Benedict's test:

For reducing substances in urine, including glucose, Vit.C , salicylates,...
Is non specific, is of no real value.

b) Glucose oxidase Strip:

Is specific to glucose in urine, but low renal threshold give positive result in spite of normal blood glucose.

II – Blood

a) fasting blood sugar : (8 – 12 hours fasting):

- Normal fasting blood sugar is 70 – 110 mg%.
- If more than 120 gm% , may suspect diabetes specially in hyperthyroidism.
- Normal fasting blood glucose doesn't exclude diabetes.

b) Two hours post prandial blood sugar:

Normal level is below 140 mg%, level above that may suspect diabetes.

- If glucose level comes between 120 – 180 mg% is borderline diabetic, may develop diabetes in future.
- If above 200 mg% is diabetic.
- The patient should receive 75 – 100 gm glucose in 250 ml water 2 hours before test.

c) **Oral glucose tolerance test:**

- Is the ability of body to utilize glucose without appearance of hyperglycemia or glucosuria.
- The test is used in diagnosis of diabetes in cases of normal fasting glucose level or borderline diabetes.

- Procedure:

- The patient should be fasting , no tea or coffee, except water.
- Fasting sample of blood and urine are analysed.
- Allow the patient to take 100 gm glucose (1.5 gm/ kg) in 250 ml water.
- Four samples of blood and urine should be analyzed in 1/2 , 1, 2,3 hours , then outline curve for diagnosis (Time with blood glucose values).

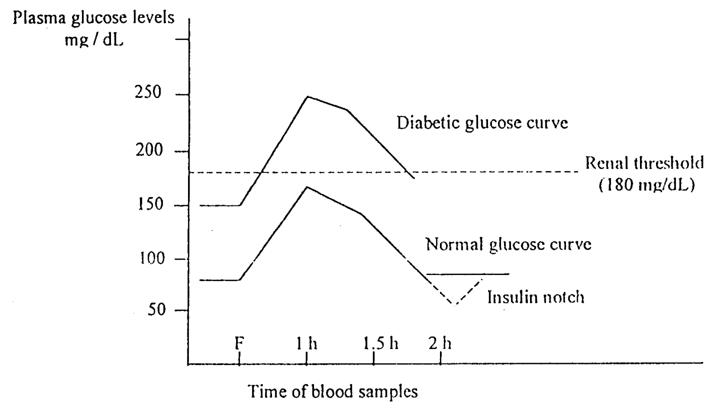
- In normal cases:

- Fasting level is within normal.
- Blood sugar level rises to its maximum in one hour (130 – 140mg%) due to absorption of glucose.
- Then blood glucose attains its fasting level (70-120%) in about two hours due to rapid utilization of glucose by insulin secretion.
- All urine samples are negative to glucose.

- In diabetic cases:

- Fasting level is above normal (above 140%).

- It reaches its maximum level in prolonged time (1.5 – 2 hours) , is more than 200 mg%.
- Then it begins to attain its fasting level slowly in 3 – 4 hours due to poor utilization of glucose by the impaired insulin.
- There is glucosuria if blood glucose is above the renal threshold (180 mg%).



d) Glycosylated Hb A1c : for follow up:

- A major component of Hb in red cells is Hb A1, which undergoes glycosylation with gluose into A1a , A1b , and A1c , in which glucose is

attached to N. terminal valine residue in the B chain of Hb → glycosylated Hb.

- Glycated Hb is formed due to exposure of Hb in RBcs to high glucose at long periods.
- The test gives idea about the diabetic patient, its control in the last 2 months (Red cell life span).
- Hb A1c, is increased in mal control of diabetes.
- Its normal level is 2-5% of total Hb.

e) Glycated serum glycoproteins fructosamine:

- Is other approach to evaluate glucose control in the previous 2-3 weeks, so it gives a more rapid indication in change of diabetic control.

Neonatal hypoglycemia

Blood glucose level is below 40 mg%

- Causes

(1) infants born to diabetic mothers :

- placental hyperglycemia causes hyperplasia of fetal pancreatic B.cells → hyperinsulinemmia → hypoglycemia after birth due to increase amounts of insulin.
- Also subcutaneous fat is increased due to stimulation of lipogenesis.

(2) Small for dates infants prematurity, toxemia of pregnancy, or the smaller of the twins → hypoglycemia:

- In these situations there is depletion of liver glycogen and loss of subcutaneous fat.

- Signs :

- Convulsions , tremors, attacks of apnea with cyanosis.

- Management:

- 10 – 20 ml 10% glucose I.V , blood glucose should be kept above 40 mg%.

Special Terms

- Glycosuria :

Is presence of abnormal amounts of any sugar in the urine.

- Glucosuria :

Is presence of glucose in urine (above 30 mg%), which can be detected by benedicts test.

Causes :

(1) **Hyperglycemic glucosuria:**

- Diabetes mellitus.
- Increase adrenaline secretion in stress or phoechromocytoma.
- Alimentary glucosuria.

(2) **Normoglycemic (Renal glucosuria):**

- Low renal threshold (diabetes innocens)
- Due to congenital renal defect.
- Acquired renal disease (nephritis).
- Pregnancy glucosuria: occures in 20% at all pregnancies , due to decrease renal threshold, it becomes normal after labour.

- Fructosuria :

- Due to ingestion large amounts of fructose.
- Hereditary deficiency of furctokinase.

- Pentosuria :

- Due to ingestion large amounts of pentose as in grapes and cherry.
- Due to deficiency of L- xylulose.

- Lactoseuria :

- In late months of pregnancy and during lactation.

LIPID METABOLISM

- Adult man ingests about 60 – 150 gm of lipids pr day.
- Triacylglycerol forms about 90% of lipid diet, the rest is phospholipids, cholesterol and fat soluble vitamins.

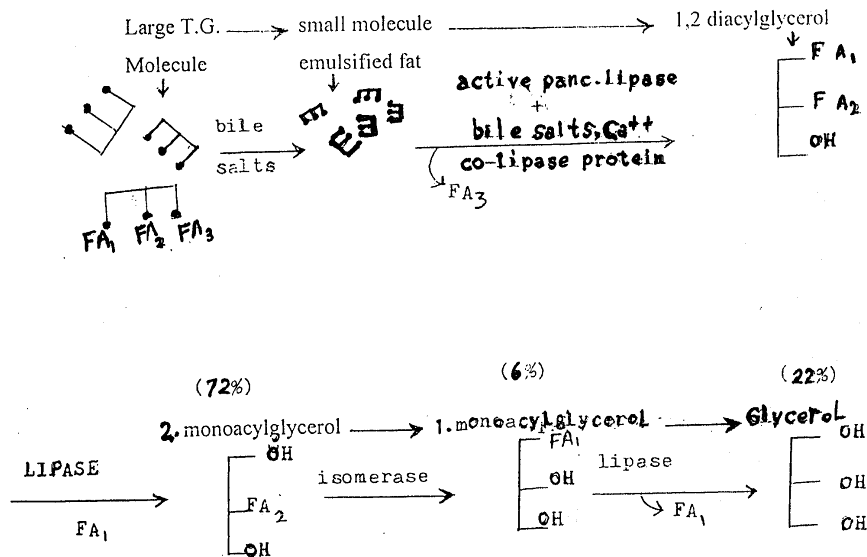
Importance:

- Lipids are one of the main sources of energy to body.
- Supply body with essential fatty acids, and fat soluble vitamins (A,D,E and K).

Sources:

1) In plant oils 2) Animal fat : lard &butter

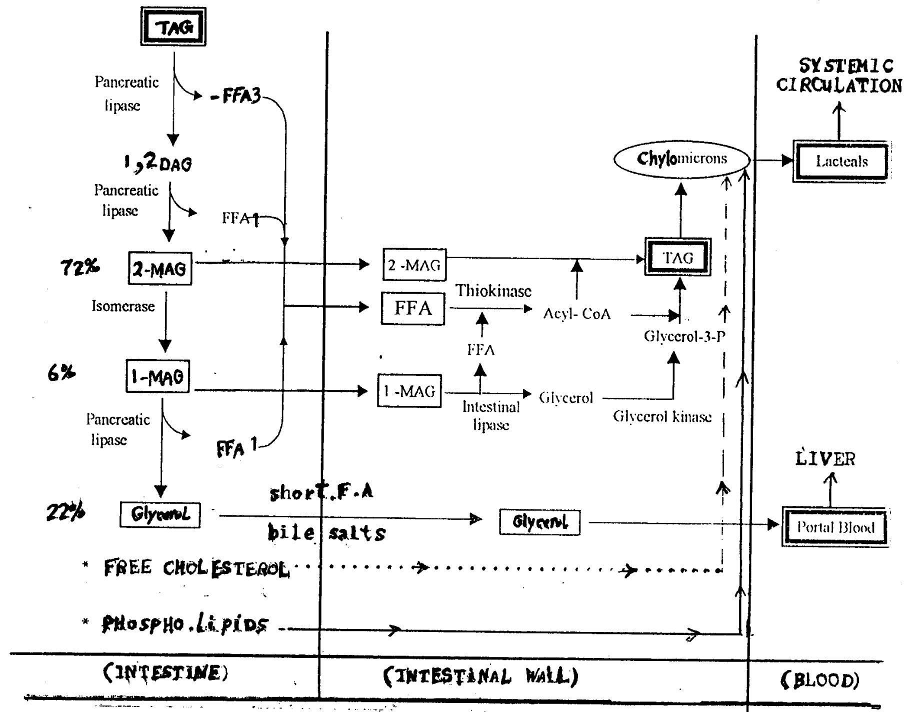
Digestion:



I) Triacylglycerol:

- Ingested triacylglycerol are emulsified with bile salts (breakdown of large fat molecules into small ones to increase their surface area), and then undergo enzymatic hydrolysis by different lipase enzymes.
- **Lingual lipase (pH 3-6):**
  In mouth by sublingual lipase, but is non significant, because diet passes rapidly to stomach.
- **Gastric lipase (pH 3-6):**
  In stomach, triacylglycerol (T.G) is acted upon by gastric lipase in first 15min only, because it inhibited by gastric Hcl (pH 1-2).
  But in infants its action is prolonged due to low gastric acidity (acts on short & medium chains of milk fats).
- **Pancreatic lipase (pH 8):**
  In small intestine T.G. is acted upon by the strong pancreatic lipase which is activated by bile salts and Ca^{++}.
- Co-lipase is protein excreted from pancrease aids binding of lipase to its lipid substrate.
- Fatty acid at position 3 is separated first → 1,2 diacyliglycerol, then fatty acid at position 1 → 2 monoacyl glycerol.
- 2 monoacylglycerol is not separated by pancreatic lipase, so is transformed into 1.monoacylglycerol by isomerase ezyme.
- 1.monoacylglycerol is attacked by pancreatic lipase → glycerol + fatty acid.

Diagram for Digestion and Absorption of TAG

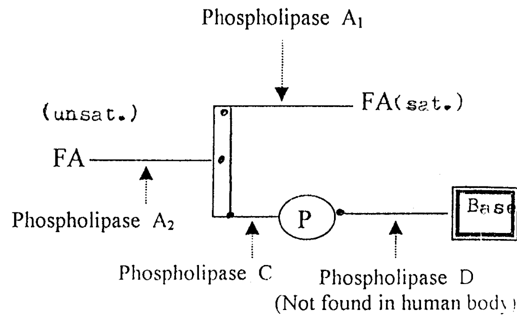


So, end products are:

- 2.monoacylglycerol (72%).
- 3.Fatty acids and glycerol (22%).
- 1.monoacylglycerol (6%).

II) Phospholipids:

- Are conjugated lipids, formed of: glycerol, two fatty acids (sat. and unsat.), phosphoric acid, base [choline or colamine].
- Phospholipids are digested by intestinal phospholipases (A_1, A_2, C and D) with aid of bile salts, and Ca^{++} ions to yeild its free compounds.



III) Cholesterol:

- Free cholesterol is not digested, but absorbed as such with bile salts.
- Cholesterol ester, undergoes hydrolysis by cholesterol esterase liberating the free cholesterol and fatty acid.

Now, the end products of all lipids digestion are:

1) 2. monoacylglycerol, long chain fatty acids (palmitic, stearic, oleic, ...), cholesterol, phosphoric acid, and bases, are mixed with bile salts render them water soluble by decreasing their surface tension to be easily absorbed, this mixture is called micelles.

2. Short chain fatty acids (caproic, butyric), glycerol, and bile salts are absorbed → portal blood → liver where they utilized.
   Bile salts are re-excreted in bile (enterohepatic circulation).

Absorption:

- Micelles are absorbed through the mucosal cells with aid of bile salts.
- In mucosal cells, long chain fatty acids are activated to acyl-CoA by thiokinase, CoA sH, and ATP, then combine with 2.monoacylglycerol forming T.G. again in presence of acyltransferase (resynthesis).
- Phospholipids are also resynthetized in the mucosal cells.
- Cholesterol is also re-esterified by acyl-CoA → cholesterol ester.
- Triacylglycerol, phospholipids, and cholesterol ester are bound to a protein [Apolipoprotein B48] in mucosal cells to form the soluble lipoprotein chylomicranes, which enter lacteals and thoracic duct to reach the systemic circulation.
- Chylomicrones are milky appearance, and produce turbidity of plasma, which is cleared by the lipoprotein lipase [clearing factor].

Steatorrhea (fatty diarrhea):

- Is condition which fat content of stool is increased (more than 5gm/day) due to deficiency of:
  1) Pancreatic lipase in chronic pancreatitis.
  2) Bile salts in chronic cholecystitis and bile duct obstruction.
  3) Unhealty endothelium (sprue) which decrease absorption of lipids.

DISTRIBUTION OF BODY LIPIDS

Body lipids are distributed as:

1) Depot fat (adipose tissues).
2) Tissue lipids (cell membranes).
3) Plasma lipoproteins.
4) Bone marrow lipids (pure lipids).

I – Depot fat
(Adipose tissue)

Source:

- Fat of diet.
- Excess carbohydrates intake (lipogenesis).

Site:

- In cytoplasm of adipose tissues as yellow droplets cells rich in triacylglycerols which are riched in saturated & unsaturated fatty acids.
- Present under skin, breast, omentum (obesity) and around organs as kidney.
- Its amount is variable; is increased by over feeding, and is decreased by fasting.

- **Function:**

- Depot fat acts as source of energy during fasting (1gm Fat → 9.3k.cal; in vitro and one gm / mole palmitate → 129 ATP in vivo while carbohydrates → 4.1k.cal/gm. In vitro

- 7.dehydrocholesterol in adipose tissue under skin $\xrightarrow{U.V}$ Vit D_3.

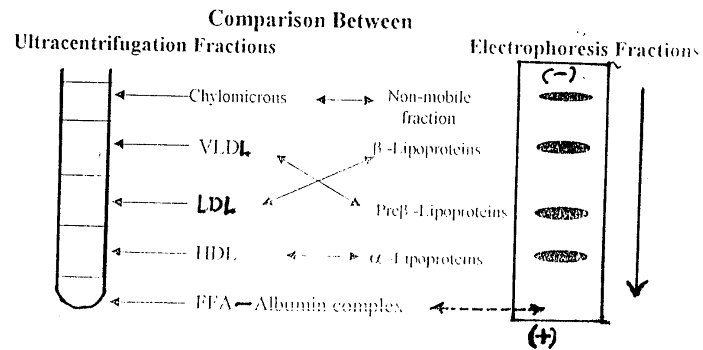
- Depot fat helps fixation of some organs as kidneys.
- Protects against trauma, acts as isolator in cold.
- Triacylglycerol amount is controlled by two processes, lipogenesis and lipolysis.

Brown adipose tissue:

- Brown adipose tissue is brown in colour due to its high content of mitochondria, cytochromes and rich in blood supply.
- It is involved where heat generation is necessary.
- It shows decreased amount of ATP production due to low activity of ATP synthase, and presence of uncoupling thermogenin protein in mitochondrial membrane which acts as a proton gate, so, heat is generated instead of ATP production.
- Brown adipose tissue is involved in animals exposed to severe cold atmosphere for warmness.
- Some humans rich in brown adipose tissue can eat and not get obesity, because energy is released as heat, not as ATP which is required for lipogenesis.
- Therefore, brown adipose tissue is reduced or absent in obese persons.

II – Tissue lipids

- Enter in structure of all cell membranes for integration of the cell.
- It never be oxidized to give energy.
- Cell membrane is hydrophobic contains phospholipid bilayer (35%), and cholesterol (5%) associated with proteins as (proteolipids).



Classes, composition, and function of plasma lipoproteins

Classes Ultracentrifugation (Density)	Total proteins % (Apolipoproteins)	Total lipids	T.G.	Cholest Ester	Cholest	Ph. Lipid	Size of molecule (nm)	Source	Function
Chylomicrones	(1%): B-48, C, E, A	99 %	90	3	1	6	150-1000	Diet	Transfer lipid diet to liver adipose tiss. and peripheral tissues
VLDL (pre β lipoprotein)	(10%): B-100, C	90%	60	14	6	20	30-70	Liver	Transfer T.G from liver to tissues, give rise to LDL
LDL (β lipoprotein)	(20%): Apo, B100	80%	18	45	10	27	17-26	VLDL	Major carrier of cholesterol from liver to peripheral tissues
HDL (α lipoprotein)	(45%): •Apo-A, C, E in liver In plasma: •Apo-A_1 (75%) A_2 (25%)	55%	15	30	10	45	7-9	Liver	•Remove cholest. From peripheral tiss. to liver. • Stim. LCAT

* Apo A_1 : Activator of LCAT   * Apo C_{11} : Activator of lipoprotein lipase in chylomicrons

:* Apo B, E : Recognition of lipoproteins by its cell receptors

III – Bone marrow lipids

- Are pure lipids in long bone cavities, if crush occurs → escape of lipids to circulation, may lead to fat emboli , bone marrow is the site of heme biosynthesis (85%).

IV – Plasma lipoproteins

- Absorbed lipids are water insoluble and to be transported and distributed to various tissues, should be hydrophilic (soluble).
- Therefore, lipids are conjugated with apoproteins by physical bond where the protein is hydrophilic → soluble lipoproteins.
- Apoproteins are synthethized mainly in the liver.
- Failure of apoproteins synthesis in liver prevent mobilization of fat from liver → fatty liver.
- The central core of lipoproteins are formed of non polar lipids as cholesterol ester and triacylglycerol. The outer layer contains more polar lipids as (phospholipids) and apoproteins.

Classes of plasma lipoproteins:

- Main four classes of plasma lipoproteins are identified by separation with electrophoresis [according to charge and molecular weight].
- OR by ultracentrifugation (according to density of protein fraction).
- Each class of plasma lipoprotein contains all types of lipids (T.G. cholesterol, and phospholipids) in addition to various apoproteins in different ratios.
- For types, composition, sources, function and fate ….. look the table.

Metabolism of lipoproteins:

I) Chylomicrons: (is carrier of exogenous T.G.)

its function is to carry lipid from diet to liver & peripheral tissues.

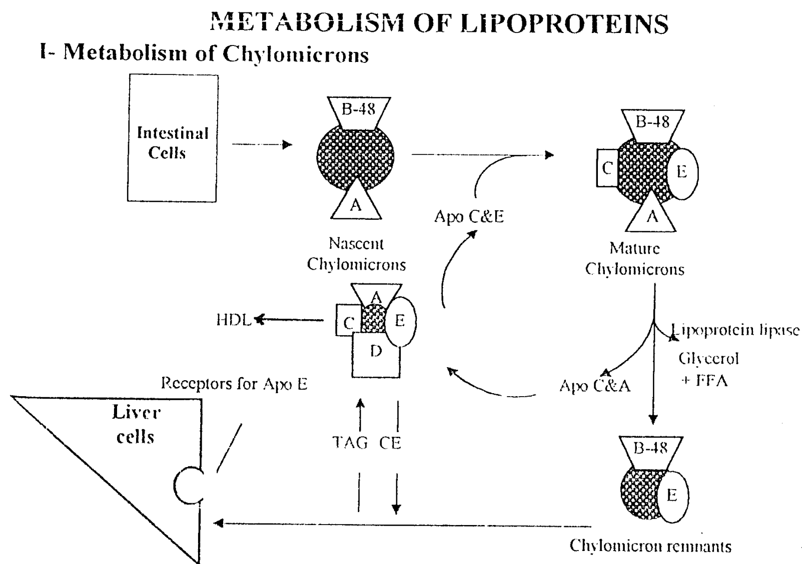
1. Synthesis of nascent chylomicrons:
   - Chylomicrons produced in intestinal mucosa contain mainly T.G. in addition to phospholipids and cholesterol esters.
   - This particle is called nascent (newly synthesized) chylomicrons and contain Apo.B48 (synthesized in intestine, is 48%large as Apo.B100) and represent 48% expression of Apo.B gene. Apo B48 causes chylomicrons secretion from intestine.
   - Nascent chylomicrons are drained by intestinal lacteals to the thoracic duct, then to blood stream.
2. Conversion of nascent to mature chylomicrons:
   - In blood nascent chylomicrons receive Apo CII, E, A from HDL (Apo CII → stimulates lipoprotein lipase, Apo E→ for recognition of hepatic cells to remnants chylomicrons) to change into mature chylomicrons.
3. Degradation of mature into remnants chylomicrons:
   - About 90% of T.G in mature chylomicrons is hydrolysed by lipoprotein lipase (secreted by capillary walls of adipose tissues, cardiac, skeletal and mammary glands, is stimulated by Apo CII), therefore the molecule is shrinked and called remnant chylomicrons (is half diameter of mature one). Hydrolysed fatty acids are carried on albumin and may be oxidized in peripheral tissues, or uptaken by liver cells.

- Lipoprotein lipase is activated by heparin and it is called clearing factor , insulin enhances its synthesis.

4. Uptaking of chylomicrons remnant by the liver:
   - After hydrolysis of T.G. in mature chylomicrons into remnant, Apo C, A are transferred to HDL.
   - Also, T.G. in chylomicrons into remnant is transferred to HDL in exchange with cholesterol esters with aid of Apo D.
   - Hepatic lipoprotein receptors recognize upon the chylomicron remnant through the Apo E, B48 and taken by its endocytosis to the lyzosome where the molecule is hydrolysed into fatty acids, free cholesterol and amino acids, or reused for synthesis of lipoproteins.
   - The cholesterol released from dietary chylomicrons regulates the cholesterol synthesis via inhibiting the HMG COA reductase in the liver.

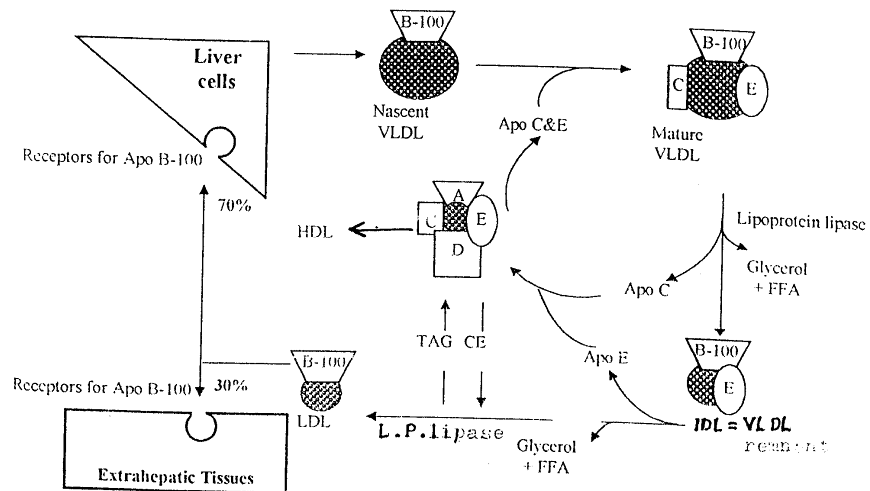
METABOLISM OF LIPOPROTEINS

I- Metabolism of Chylomicrons



II) **<u>Metabolism of very low dense lipoproteins (VLDL)</u>:** (is - carrier of endogenous T.G.)

- Its function is to carry T.G. formed in the liver to peripheral tissues where they oxidized (utilized) or stored in adipose tissue as T.G., also give rise to LDL.
- Nascent VLDL is synthetized by liver cells, and contains Apo B100 [synthetized in liver, is the longest single polypeptide chain known; about 4536 amine acids]. Apo B100 causes VLDL secretion from liver
- Nascent VLDL receives Apo-C E from HDL in the blood to form the mature VLDL.
- T.G. in mature VLDL is hydrolysed by lipoprotein lipase as in chylomicrons liberating its free fatty acids for utilization or storage, and the mature VLDL is shrinked into VLDL remnant or [IDL] = [LDL1]
- Apo.C is returned back to HDL.
- VLDL remnant [IDL] is converted into LDL by further hydrolysis of its T.G. by lipoprotein lipase . Apo E is returned back to HDL.
- Also T.G is transferred to HDL in exchane with cholesterol esters via Apo-D.



-VLDL METABOLISM-

&

-LDL METABOLISM-

III) Metabolism of low dense lipoproteins (LDL):

- LDL is arised from VLDL, where it contains high percentage of cholesterol & cholesterol ester, about 55%.
- LDL form about 50% of all lipoprotein classes, is called bad cholesterol.
- The main apolipoprotein in LDL (β lipoprotein) is designated B
- LDL binds to specific glycoprotein Apo B-100 receptors in both liver (70%) and peripheral tissues (30%) for utilization.

- In liver:

LDL binds to its receptors, and by endocytosis is transported to lysozome where it destructed giving rise to free cholesterol which may give rise to bile salts, also phospholipids, fatty acids, and amino acids are liberated, liver is the main channel for excretion of cholesterol as bile salts in intestine.

- In peripheral tissues:

It binds to its LDL receptors

- In gonads: It gives rise to male & female sex hormones.
- In supra renal cortex: Gives rise to glucocorticoids, and mineralocorticoids.
- In skin: Gives rise to 7. dehydrocholesterol $\xrightarrow{U.V.}$ vit. D_3.
- Excess LDL may be precipitated in injured blood vessels → atherosclerosis.

- Also, atherosclerosis may arised in defective receptors in cases of familial hypercholesterolemia.
- Atherogenesis: is arised by exposure of excess amounts of LDL to oxidants (free radicals) → oxidized (modified) LDL which causes transformation of macrophages in C.T. of arterial wall into foam cells → accumulation in arterial walls → release growth factors → smooth muscle proliferation → atheromatous plaque.

Antioxidants like vitamin C & E reduce atherosclerosis.

IV) Metabolism of high dense lipoproteins (HDL):

Site of synthesis:

- HDL is synthetized in the liver as discoidal HDL, is the smallest size lipoprotein (7-9 nm).

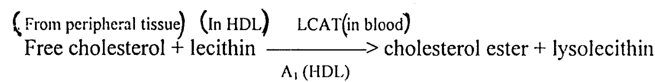
Structure:

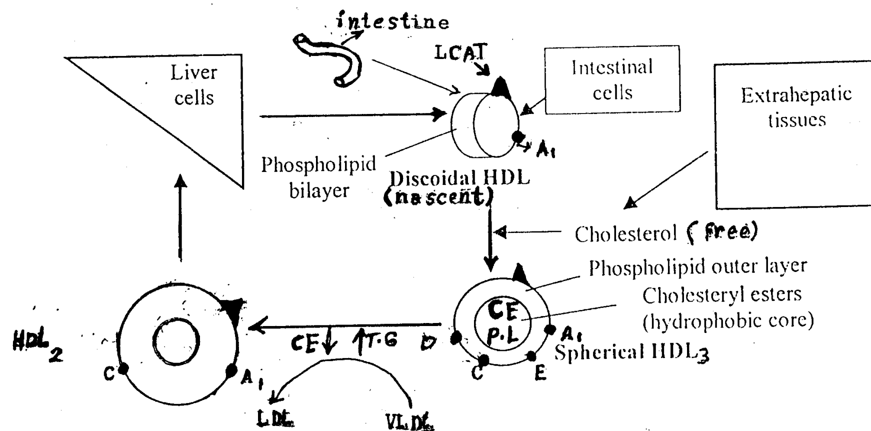
- It contains the highest percentage of apoproteins; about 45%.
- The main apolipoprotein in HDL (α lipoprotein) is designated A

- HDL_I (discoidal) : A_I = nascent form
- HDL_2: A_I: 85%, A_2 15%, C: 4%
- HDL_3: A_I: 75%, A_2: 20%, C: 4%, D: 1%, E: 0-5% = mature form
- Apo A_I : is activator of LCAT, while Apo A_2 is inhibitor of Apo A_I & LCAT
- HDL contains the highest content of bilayer phospholipids (about 45%) but small percentage of T.G. and cholesterol.

Functions:

- HDL acts as scavenger of free cholesterol from peripheral tissues, cell surfaces, and other circulating lipoproteins (in blood vessels), and send it to liver.
- Once free cholesterol is taken up by HDL is esterified into cholesterol ester via HDL phospholipid (lecithin) and plasma LCAT enzyme (lecithin cholesterol acyl transferases).
- Apo-A_I in HDL stimulates LCAT.

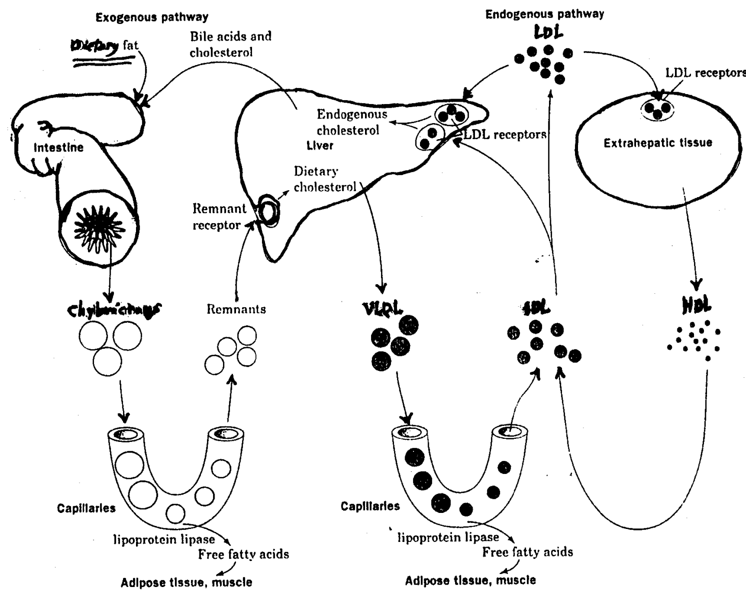




- So, LCAT-HDL system protects cell membranes from damaging effect of free cholesterol.
- Cholesterol ester formed in HDL pushes the phospholipid bilayer apart and converts the discoidal HDL into the spherical HDL [HDL_3].
- HDL acts as reservoir for Apo C,E for proper metabolism of chylomicrons and VLDL.
- Cholesterol ester is partly transported to IDL (in exchange with T.G., Free cholesterol to form LDL.

Fate:

- HDL [HDL_2] is phagocytosed by the liver cells, and in lysozome cholesterol ester is hydrolysed into free cholesterol which is either reused in lipoproteins or converted to bile salts where it excreted in bile to intestine.
- So, HDL_2 is important for removal of cholesterol from the tissues to the liver, and high levels of HDL protect against atherosclerosis, the mature HDL is called the good cholestrerol.


Exogenous pathway
Dietary fat
Bile acids and cholesterol
Intestine
Endogenous cholesterol
Liver
LDL receptors
Dietary cholesterol
Remnant receptor
Remnants
Capillaries
lipoprotein lipase
Free fatty acids
Adipose tissue, muscle
Endogenous pathway
LDL
LDL receptors
Extrahepatic tissue
HDL
Capillaries
lipoprotein lipase
Free fatty acids
Adipose tissue, muscle

** Lipoprotein (a):

- Is similar in composition to LDL, but has higher protein content
  (has extra protein portion similar to plasminogen and is attached to Apo B100 by disulfide bond), so it migrates by electrophoresis more rapidly than LDL.
- Lipoprotein (a) is synthetized in liver, is genetically determined, and raised in familial hypercholesterolemia.
- Lipoprotein (a) increases in risky patients with ischemic heart diseases, and in genetic family heart diseases, even if have normal lipid level.
- It interferes wit fibrinolysis → may induce thrombosis if increased.
- It binds to fibrin → promote plaque formation.

Disorders of plasma lipoproteins:

I) Hypolipoproteinemia:

1) Abetalipoproteinemia:

- Is rare genetic disease, in which B-lipoprotein (LDL), chylomicrones and VLDL are absent due to inability to synthetize apoprotein B100 (absent Apo B gene).
- Fat absorption is inhibited → steatorrhea.
- There is also retinitis due to malabsorption of vitamin A.
- Treatment:
  Large doses of fat soluble vitamins, specially vit.E.

2) Familial α-lipoprotein deficiency (Tangier disease):

- Is rare autosomal disease (autosomal gene), in which α-lipoprotein (HDL) is 1-5% of its normal level due to Apo A deficiency.
- Plasma cholesterol and phospholipids are diminished.
- Cholesterol esters are accumulated in lymphoid tissues as tonsil (enlarged, orange reddish due to deposition of cholesterol ester).
- There is also hepatosplenomegaly.

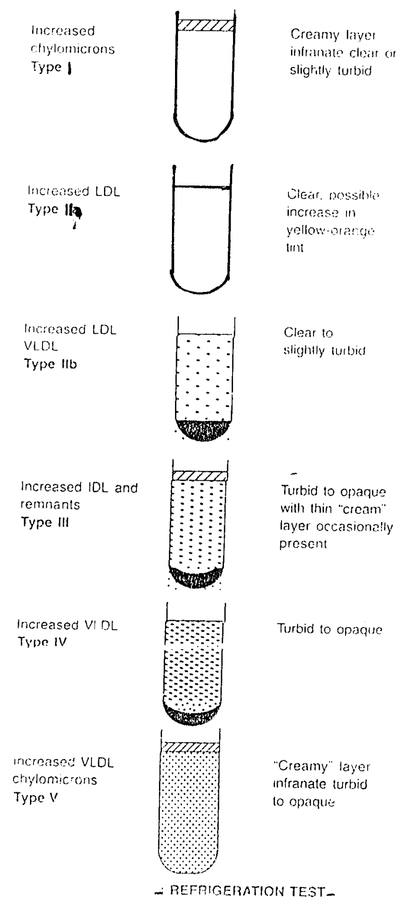
II) Familial hyperlipoproteinemia:

1) Type I hyperlipidemia:

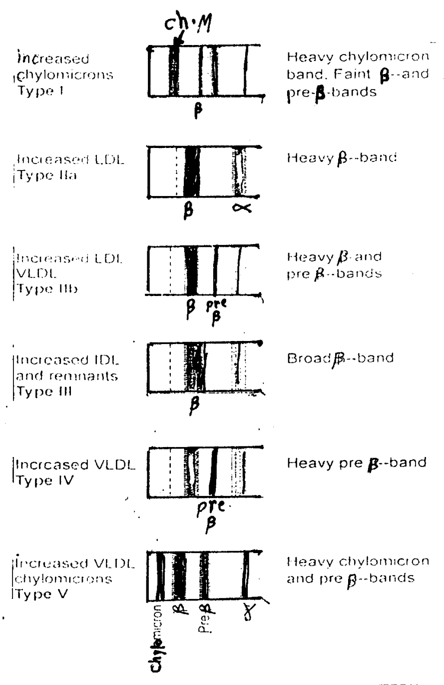
- In which genetic defects in lipoprotein lipase or Apo CII [activator of lipoprotein lipase] is present.
- Patients with type I show marked elevation of chylomicrons after fatty meal [Triacylglycerol is over 1000mg%, normally is up to 140mg%], it shows slow clearance.
- There is eruptive xanthomas of triglycerides, and pancreatitis, but no increased risk of coronary diseases, cholesterol is within normal level.
- Plasma is milky appearance, and there is turbid floating layer if sample left overnight.
- The condition is treated by restriction of fat diet.

2) Type II hyperlipidemia:

- Is most common, characterized by increased LDL (hypercholesterolemia) due to defect in LDL receptors, so not stored in liver or utilized in peripheral tissues → increase plasma LDL.
- Atherosclerosis: is developed → heart and cerebral risks.



– REFRIGERATION TEST –



– LIPOPROTEIN ELECTROPHORESIS PATTERN –

- In familial homozygous patients have very high LDL levels, and may suffer myocardial infarction before age 20 years.
- There is two subtypes:

  Type II a: there is increased LDL only

  Type II b: there is increased LDL and VLDL (TG).
- Hypothyrodism may be associated.
- Condition is corrected by restriction of cholesterol diet or saturated fatty acids, and replacement with polyunsaturated fatty acids as corn & sunflower oils.

3) Type III hyperlipidemia:

- Characterized by increase LDL& VLDL (β.pre β) lipoproteins → broad β band by electrophoresis.
- The defect is due to abnormality in Apo E → decrease clearance of chylomicrons & VLDL remnants (not taken by Apo E receptors on liver).
- Patients suffer from atherosclerosis, coronary, and peripheral diseases.
- The case can be corrected by weight reduction, and diet should contains low carbohydrates and cholesterol diet, but increased unsaturated fatty acids uptake.

4) Type IV hyperlipidemia:

- Is commonest type characterized by overproduction of VLDL, may associated with diabetes Type II and hyperinsulinemia (may be the cause of VLDL over production), coronary heart disease is associated.

- Insulin stimulates lipogenesis and lipoprotein lipase synthesis which acts on VLDL, s in diabetes VLDL is not acted upon by lipoprotein lipase → increase VLDL.
- Obesity and alcohol abuse may be associated.
- LDL & HDL are within normal range or subnormal, but triacyl-glycerol is increased.
- The condition can be corrected as type III.

5) Type V hyperlipidemia: (unknown cause)

- Characterized by elevated chylomicrones and VLDL.
- Plasma T.G. and cholesterol are elevated.
- Obesity and pancreatitis may be associated.
- Increased risk of coronary heart disease in some patients.
- The condition may be corrected by weight reduction.

Secondary hyperlipoproteinemia:

- Is due to other diseases:
  1) Diabetes mellitus.
  2) Obstructive jaundice.
  3) Hypothyroidism.
  4) nephrotic syndrome.
  5) Obesity.

PLASMA LIPOPROTEINS AND ATHEROSCLEROSIS

Atherosclerosis can be arised due to increased concentrations of plasma cholesterol and triacylglycerol, so LDL & VLDL are atherogenic if elevated, but chylomicrones are not atherogenic.

Factors affecting plasma lipids & lipoproteins:

I) Diet:

1) Lipids:

a) Cholesterol rich diet and saturated lipids → increase plasma LDL and cholesterol (100mg cholesterol intake →↑ plasma cholest. by 5mg/dl.)

b) Polyunsaturated oils (ω^3 oils: fish oils, linseed oil, and walnut, corn oil) → decrease plasma LDL and cholesterol.

c) Monounsaturated F.A (olive & peanut oils) → increase HDL.

2) Carbohydrates:

- Excess carbohydrates intake (more than 75% of total calories; normal intake is about 60%) → increase triglycerides (lipogenesis).
- Also, sucrose & fructose intake increase plasma triacylglycerol to great extent, because fructose escape two steps in glycolysis → yielding excess acetyl CoA → increase T.G. and cholesterol.

3) Increased total caloric intake:

- Increase total food intake → weight gain, and increase T.G. and VLDL.

4) Alcohol:

- Heavy alcohol intake → stimulate lipogenesis → increase T.G.
- Moderate alcohol intake → increase HDL concentration due to increased induction of $ApoA_1$ synthesis.

5) Smoking (nicotine), and emotion stress, stimulate lipolysis:

→ increase free fatty acids → increase acetyl CoA → increase T.G. and cholesterol.

II) Drugs:

1) **Contraceptive pills (estrogen & progesterone):**

- Lead to increase in T.G, cholesterol, LDL, and VLDL in 50% of middle age female (20-40%), but HDL not changed.

2) • Estrogen : alone in post menopausal female → decrease cholesterol, LDL, VLDL and T.G. but HDL is increased due to induction of $Apo.A_1$.

3) • Nicotinic acid: → decreases lipolysis → decrease FFA → decrease VLDL and cholesterol, and may increases HDL.

III) Sex:

Normal values in females is slightly increased than males.

IV) Age:

Normal values are increased with age. Total cholesterol (female: 160-230mg%, male: 155-220mg%).
This value is from age 20-70y, and increases by 10mg% every 5 years roughly.

There are some factors which precipitate atherosclerosis and coronary heart diseases as: smoking, diabetes, hypercholesteremia, hypertension, senility, obesity and decrease HDL.

Proper mixed oils for health:

One volume of monounsat. F.A (olive oil) with two volumes of polyunsaturated F.A. (corn oil, sunflower, or cotton oil).

This mixture leads to increase in HDL, and decrease in LDL.

** **ω^3 (omega.3) (Fish oils):** Present in fish oils, is polyunsaturated F.A → decreases T.G, cholesterol, and decreases platelets aggregation.

Mechanism of developing atheromatous plaque:

- Chylomicrones are not atherogenic, because of its large size, can't enter the intima of arterial wall.
- LDL & VLDL are atherogenic, they are smaller in size, and can pass the intima and adhere to elastin layer if there is damage to intima of blood vessels.
- Apo.B in LDL &VLDL has affinity to adhere to elastin layer in the damaged artery.
- White cells accumulate at site of injured arterial wall, they contain scavenger receptors which bind the oxidized cholesterol and damaged materials.
- Then, white cells are transformed into cholesterol Laden-foam cells —> aggregate → plaque formation.
- Dermatan. SO_4, produced by arterial wall, if increased, may acts as receptors for developing the atherosclerotic plaque. .

HDL increases in:

Femaleness, estrogen, nicotinic acid, and regular exercise (walking at least ½ hour, or 2 miles/daily).

Risk ratio:

Total cholesterol= 4.9 mg% in male, 4.4 mg% in female (normal upper limit).

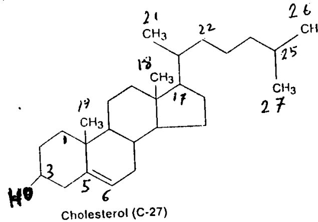
HDL

Typical fatty acid analyses of some fats of animal and plant origin.*
(All values in weight percentages of component fatty acids.)

	Saturated			Unsaturated		
	Palmitic	Stearic	Other	Oleic	Linoleic	Other
Animal fats						
Lard	29.8	12.7	1.0	47.8	3.1	5.6
Chicken	25.6	7.0	0.3	39.4	21.8	5.9
Butterfat	25.2	9.2	25.6	29.5	3.6	7.2
Beef fat	29.2	21.0	3.4	41.1	1.8	3.5
Vegetable oils						
Corn	8.1	2.5	0.1	30.1	56.3	2.9
Peanut	6.3	4.9	5.9	61.1	21.8	...
Cottonseed	23.4	1.1	2.7	22.9	47.8	2.1
Soybean	9.8	2.4	1.2	28.9	50.7	7.0†
Olive	10.0	3.3	0.6	77.5	8.6	...
Coconut	10.5	2.3	78.4	7.5	trace	1.3

METABOLISM OF CHOLESTEROL

Cholesterol is alcohol sterol of animal origin, having (– OH) group at C_3, double bond at C_5, two methyl groups at C_{10}, C_{13}, and long side chain at C_{17} containing eight carbon atoms, whole molecule is 27 carbons.



Cholesterol (C-27)

Sources:

- Exogenous:

- Diet rich in cholesterol as egg yolk (contains about 200mg), brain, liver, chicken skin, and meat.
- Normal diet intake should not exceed (300-500mg/day).
- Every 100mg of cholesterol diet → increase serum cholesterol about 5%.

- Endogenous:

- Formed mainly in liver, about 1-1.5 gm/day, which orginates from:
  - i) De-nove synthesis from active acetate.
  - ii) HDL in liver,
  - iii) Cholesterol reabsorbed from gut.

Daily loss:

- About one gm in the form of bile salts (0.5gm), and free cholesterol (0.5gm) through the bile duct.

Tissues	Efficiency of cholesterol formation (Liver = 100)
• Liver	100
• Adult skin	90
• Small intestine	60
• Gonads	31
• Kidney	4
• Adult brain	0
• Newborn brain	185

Site of formation: (in all cells)

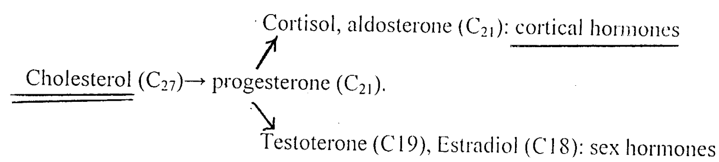
- Mainly in the liver in cytoplasm or microsomes.
- Others as skin, intestine, suprarenal cortex, gonads (ovary & testis), and aorta.

Plasma cholesterol:

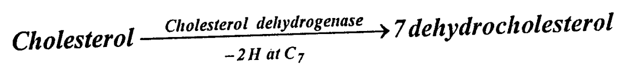
- Cholesterol in plasma is present in the form of lipoproteins = (50% of all body cholesterol, such as LDL, VLDL, HDL and chylomicrones).
- Normal total plasma cholesterol is about 120-240 mg%, is according to age (20-70 years).
- About one third (30%) is present as free cholesterol, and 2/3 (70%) as esterified form with linoleic acid usually by effect of LCAT, to be more hydrophobic.

Function:

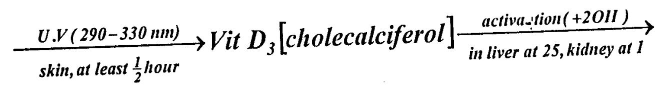
- Enter in structure of plasma lipoproteins (the esterified form), and every body cell membrane for cell integration (free form).
- **Synthesis of sex & cortical hormones:**



- **Synthesis of vitamin D_3:**



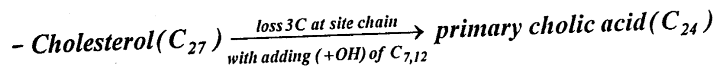
$$Cholesterol \xrightarrow[-2H \ at \ C_7]{Cholesterol \ dehydrogenase} 7 \ dehydrocholesterol$$



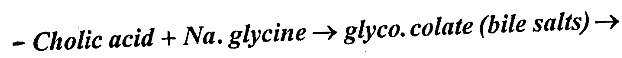
$$\xrightarrow[skin, \ at \ least \ \frac{1}{2} hour]{U.V(290-330 \ nm)} Vit \ D_3 [cholecalciferol] \xrightarrow[in \ liver \ at \ 25, \ kidney \ at \ 1]{activa.tion(+2OH)}$$

active *1,25dihydroxycholecalciferol (calcitriol)*

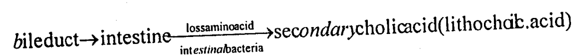
- **Synthesis of bile acids & salt: (in liver)**



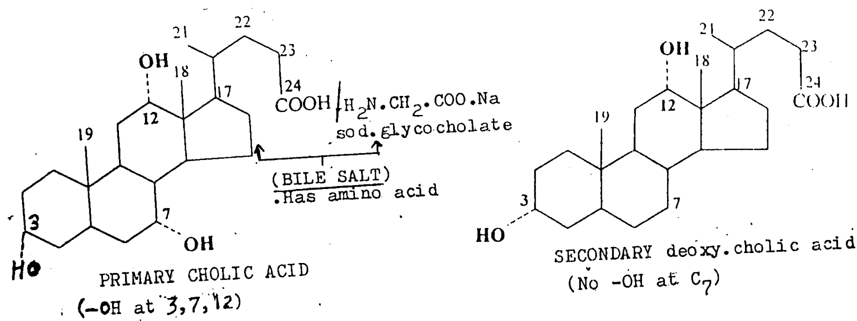
$$- \ Cholesterol(C_{27}) \xrightarrow[with \ adding \ (+OH) \ of \ C_{7,12}]{loss \ 3C \ at \ site \ chain} primary \ cholic \ acid(C_{24})$$



- *Cholic acid + Na. glycine → glyco. colate (bile salts) →*



$$bileduct \rightarrow intestine \xrightarrow[intestinal bacteria]{loss amino acid} secondary cholic acid (lithocholic.acid)$$



Excretion:

- One gram is excreted daily from the body.
- About ½ gm is excreted mainly as bile salts (its total pool in liver 3-5gm) through bile duct. In intestine amino acid is removed and converted into secondary cholic acid by effect of colonic bacteria,

about 98% of bile salts are absorbed to liver (enterohepatic circulation), bile cycle is repeated 6-10 times per day.

- Another ½ gm of free colesterol is excreted from liver → bile duct → intestine, where it converted into coprosterol (coprostanol) by effect of colonic bacteria, and is excreted in stool.
- High levels of thyroxine, estrogen, and insulin increase cholesterol excretion (due to increase bile salts synthesis) → decrease plasma cholesterol.

<u>Causes of hypercholesterolemia:</u> (above 240 mg%)

- Diet rich in cholesterol, saturated fatty acids, and carbohydrates specially sucrose and fructose (increase acetyl CoA)→ increase cholesterol synthesis.
- Hypothyrodism (myxodema) due to decrease formation of bile salts, cholesterol is 500-700 mg%.
- Diabetes mellitus (increase lipolysis → ↑ fatty acids → ↑ acetyl CoA → ↑ cholesterol biosynthesis), cholesterole is 400-550 mg% when treatment is inadequate.
- Obstructive jaundice (decrease excretion of bile salts).
- Coffee, smoking (nicotine) and stress (adrenaline) → increase lipolysis → ↑ acetyl CoA → ↑cholesterol synthesis).
- Nephrotic syndrome (type II nephritis) cholesterole is 600-700 mg%.
- Type II hypercholesterlemia.
- In coronary disease and angina (300-400 mg%).

Causes of hypocholesterolemia: (below 120 mg%)

- Diet rich in polyunsaturated fatty acids (corn, soya bean, sunflower, lin seed and cotton seed oils), all are named ω^6 PUFA ω^3 [linolenic Acid] as in fish & fish oils lowers T.G.

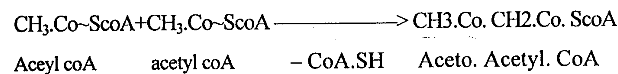
significantly than cholesterol, but has important anti-platelets aggregation effect (decrease thrombus formation).

- Prolonged fasting or starvation decrease activity of HMG-CoA reductase [key enzyme of cholesterol synthesis).
- Hyperthyroidism (thyroxine stimulates synthesis of bile salts from cholesterol), its level 80-110 mg%.
- Liver diseases.
- Cholesterol lowering drugs as lovastatin, simvastatin via inhibitory effect or HMG-CoA reductase. Also cholestyramine which prevent reabsorption of bile salts.

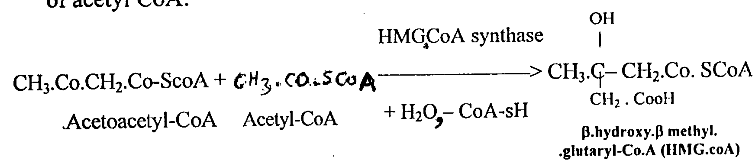
Synthesis: **occurs in all cells specially the liver, in cytoplasm:**

I- Formation of acetoacetyl CoA by condensation of two moles of acetyl-CoA:

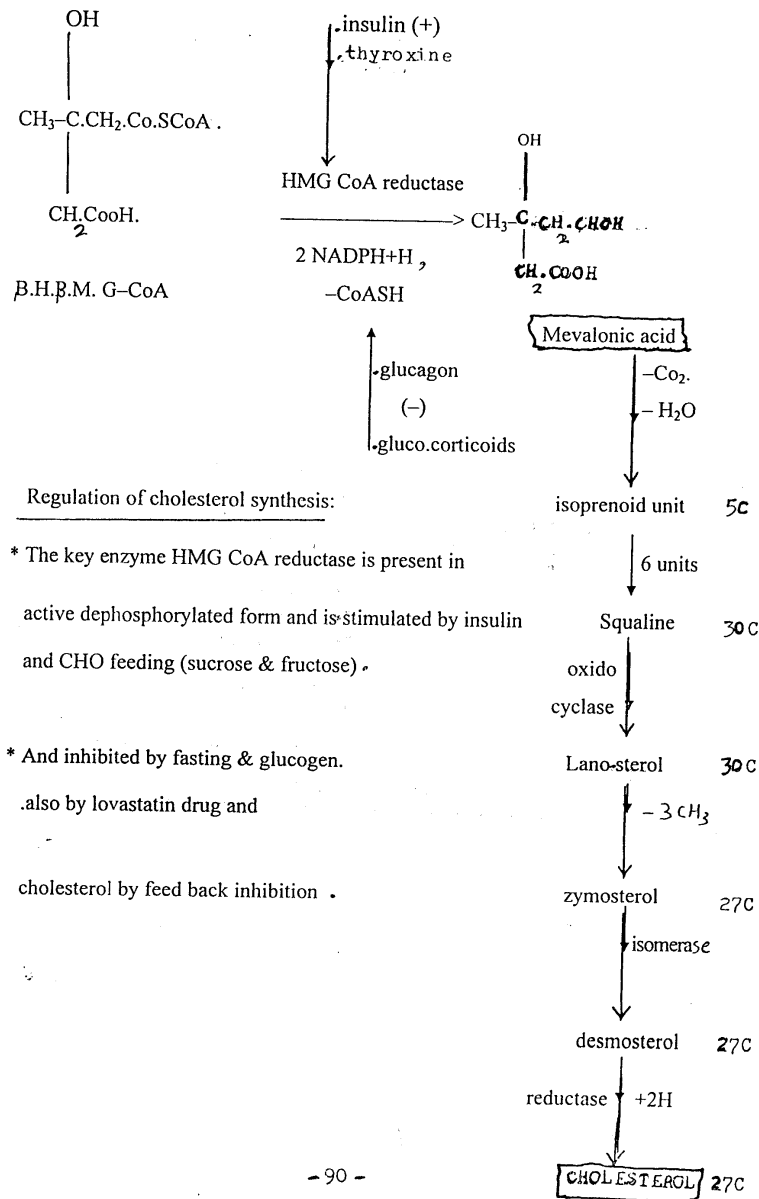
Keto. thiolase



II-Conversion of acetoacetyl-CoA into HMG.CoA, with third mole of acetyl CoA:



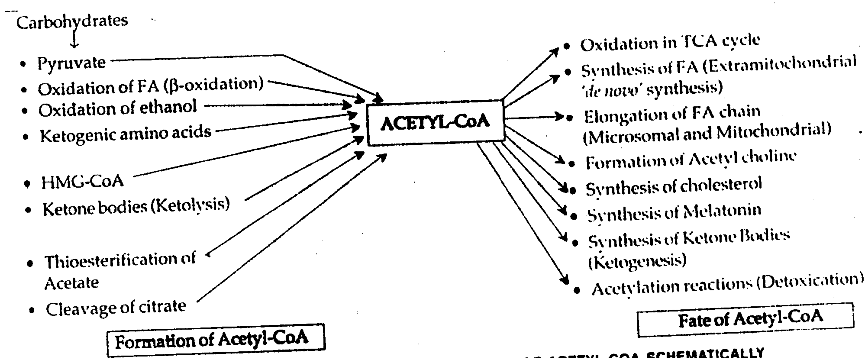
III- Conversion of HMG.CoA, into mevalonic acid and cholesterol:



Regulation of cholesterol synthesis:

* The key enzyme HMG CoA reductase is present in active dephosphorylated form and is stimulated by insulin and CHO feeding (sucrose & fructose).

* And inhibited by fasting & glucogen.
.also by lovastatin drug and cholesterol by feed back inhibition .

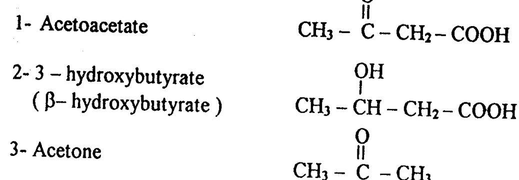


SOURCES AND FATE OF ACETYL-COA SCHEMATICALLY

KETONE BODY METABOLISM

Ketone bodies are soluble substances produced by the liver, where there is high rate of fatty acids oxidation in prolonged starvation or uncontrolled diabetes.

Types:



I – Ketogenesis (synthesis)

Site:

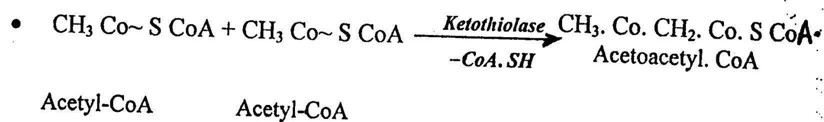
Ketone bodies are formed in mitochondria of the liver, mainly from acetyl CoA derived from fatty acid oxidation and Ketogenic amino acids, but acetyl CoA derived from glucose-pyruvate is involved in citric acid cycle to maintain it.

So, it is associated with high rate of fatty acid oxidation.

Steps of synthesis:

Require two enzymes present in the liver (HMG-CoA synthase and lyase).

1. Two moles of acetyl-CoA are condensed to form acetoacetyl-CoA.

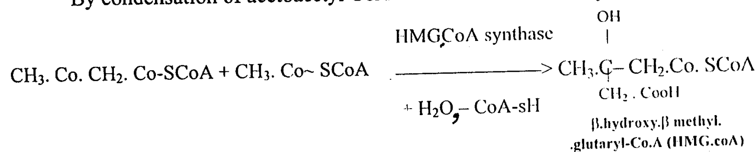


Acetyl-CoA Acetyl-CoA

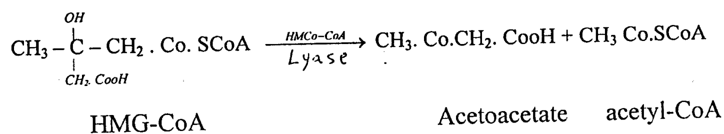
- Aceto-acetyl CoA is also produced during β. Oxidation of fatty acids in the last four carbon atoms.

2. Conversion of acetoacetyl CoA into HMGCo-A:

By condensation of acetoacetyl CoA with third mole of acetyl CoA.

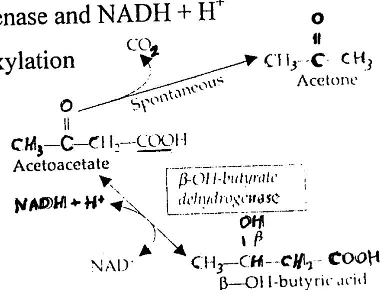


3. Conversion of HMG-CoA into acetoacetate (First Ketone body):



4. Acetoacetate is converted to β. Hydroxy butyrate by reduction with β. Hydroxy butyrate dehydrogenase and NADH + H+

Also acetone is derived by decarboxylation OF Acetoacetate.



- β. Hydroxybutyrate (2/3), and aceto acetate (1/3) are present mainly in blood and urine, but acetone is volatile, excreted in lung.

Normal level:

1 mg% in blood, less than 1 mg/day in urine.

Factors regulate ketogenesis:

1) Ketogenesis is increased in:

Fasting and prolonged starvation and uncontrolled diabetes (increase lipolysis → increase fatty acid oxidation → → ↑ketogenesis.)

- High fat, and low carbohydrate diet (increase fatty acid oxidation→↑ Ketogenesis).
- Hypersecretion of anti-insulin hormones (glucagon, adrenaline increase lipolysis).

2) Ketogenesis decreased in:

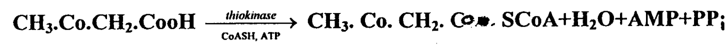
- High glucose or carbohydrate diet (glucose → acetyl-CoA → pyruvate → oxidation in citric cycle).
- Administration of insulin in diabetes (↓ lipolysis).

II – Ketolysis (Utilization)

- Excess Ketone bodies are utilized in mitochondria of extrahepatic tissues such as skeletal muscles, brain, and heart.
- Liver can't utilizes ketone bodies, because it has no acetoacetate thiokinase or CoA transferase (thiophorase) required for activation of acetoacetate.

Steps:

1. Acetoacetate is activated first to acetoacetyl CoA.



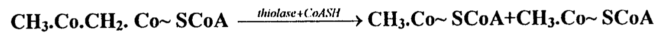
$CH_3.Co.CH_2.CooH \xrightarrow[CoASH,\ ATP]{thiokinase} CH_3.\ Co.\ CH_2.\ Co\sim\ SCoA + H_2O + AMP + PP_i$



Or: Acetoacetate + succinyl-CoA $\xrightarrow{CoA-transferase}$ acetoacetyl. CoA +

succinate (entyer citric acid cycle).

2. Acetoacetyl-CoA is splitted into two acetyl CoA by Keto-thiolase enzyme.

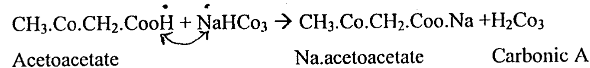


$CH_3.Co.CH_2.\ Co\sim\ SCoA \xrightarrow{thiolase+CoASH} CH_3.Co\sim\ SCoA + CH_3.Co\sim\ SCoA$

3. Acetyl CoA is oxidized in citric acid cycle to supply energy in cases of starvation, specially in brain.

* Ketoacidosis (Metabolic Acidosis):

- Increased ketone bodies in the blood is neutralized by blood buffers; mainly bicarbonate ($NaHCo_3$) → depletion of alkali reserve → acidosis, and in severe cases → coma.
- Potassium will escape from the cell to the blood → hyper kalemia (may lead to bradycardia, cardiac arrest).

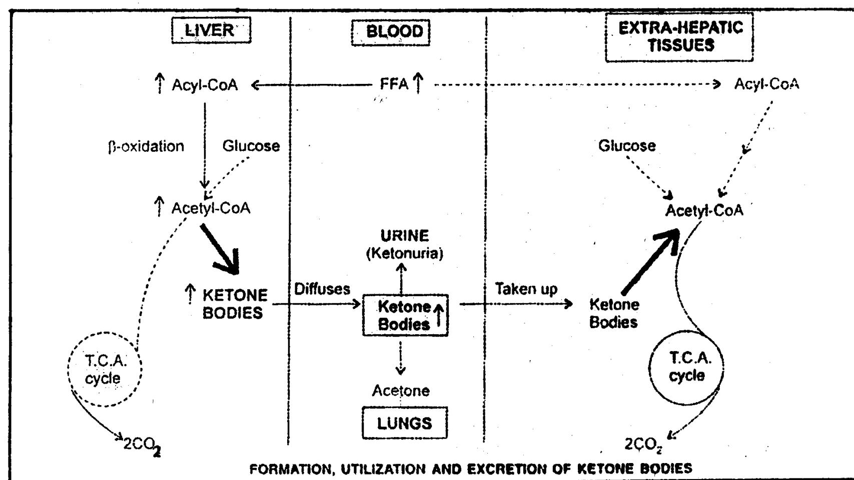


$CH_3.Co.CH_2.CooH + NaHCo_3 \rightarrow CH_3.Co.CH_2.Coo.Na + H_2Co_3$

Acetoacetate Na.acetoacetate Carbonic A

Management of Ketosis:

- Glucose administration in case of fasting and starvation.
- Insulin I.V and glucose in case of diabetes (glucose prevents sudden drop in blood glucose, and stimulate citric acid cycle to decrease dependence on fatty acid oxidation), also insulin stimulates lipogenesis → ↓ Fatty Acids



FORMATION, UTILIZATION AND EXCRETION OF KETONE BODIES

- Bicarbonate to correct acidosis.
- Potassium (KcL) supply to prevent hypokalemia produced by insulin(insulin aids transefer of K into cells).

Ketogenic substances:

- Fatty acids, and ketogenic amino acids (as leucine).
- Anti-insulin hormones (glucagons and adrenalin → ↑ lipolysis → ↑ fatty acids → ↑ ketogenesis).

Importance of ketone bodies:

- In early starvation (within 5-6 days) brain is adapted to replace 50% of glucose by ketone bodies for oxidation.
- In prolonged starvation oxidation of ketone bodies by brain reachs 95%.
- Brain can't utilizes fatty acids (can't pass brain barrier), but ketone bodies are soluble; can pass brain barrier.
- Excess fatty acids may cause cell excitability, and ventricular fibrillation, so the hydrophobic fatty acids are changed into soluble ketone bodies.
- Ketogenesis clears circulation from excess fatty acids may occur in severe starvation, and uncontrolled diabetes (increase lipolysis)are converted to soluble ketone bodies to avoid its complications .

OXIDATION OF FATTY ACIDS

It is oxidation of fatty acids in mitochondria to give maximum amounts of energy:

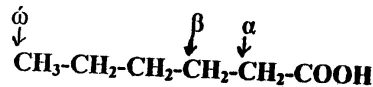
- Oxidation of one gm palmitate in vitro → 9.1 K. calory.
- Oxidation of gm/mole (256 gm) palmitate in body in vivo → 129 ATP = 980 K.calory (129 x 7.6).

  (Hydrolysis of every one ATP gives rise to 7.6 K. calory).

Types of oxidation:

1. β. Oxidation: in mitochondria: in β. Carbon atom of fatty acid, is the main route, to liberate massive energy.
2. α.oxidation in cytoplasm: in α. Carbon atom, no energy, hydroxy fatty acid is arised for synthesis of sphingolipids.
3. **Omega (ω) oxidation:**

   Oxidation in cytoplasm in terminal methyl [CH_3] group of the fatty acid, dicarboxylic acid is arised for structure of membrane of brain cells.



I – β. Oxidation of fatty acids

- The most important which gives high energy.
- Oxidation occurs in β.carbon atom of activated fatty acid (acyl-CoA).
- Two carbon atoms are removed every cycle of oxidation in the form of acetyl-CoA, which in turn is oxidized to yield 12 ATP.

Site:

In mitochondria of skeletal muscles(during rest),heart (rich in mitochondria) ,liver, kidney,adipose tissues, and lung.

- In brain fatty acids not oxidized (can't pass blood brain barrier), but only glucose or ketone bodies during starvation.
- Intracellulary, fatty acids is oxidized or stored as T.G according to energy needs..

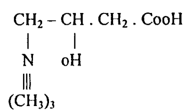
Steps:

1. Activation of long chain fatty acids in cytoplasm (microsome) → acyl CoA.
2. Transport acyl-CoA to mitochondria by carnitine carrier, (Short chains can penetrate mitochondria).
3. β. Oxidation inside mitochondria to liberate energy.

Carnitine:

- Chemistry:

It is β. Hydroxy, γ trimethyl. ammonium butyric acid



- Biosynthesis:

Carnitine arised from lysine and methionine in liver and kidneys and is concentrated in skeletal muscles and heart for their contraction .

- Distribution:

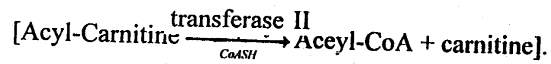
Carnitine is present in yeast, milk, lentil, and banana, also in muscles,heart, liver, kidneys and meat extracts.

- Normal ratio:

Carnitine is present in blood in small amounts (7-14 mcg/mL), in urine (50-100 mcg/mL per day).

- Function:

- Carnitine acts as a carrier molecule, it transport active long chain fatty acid from cytosol into mitochondria for oxidation.
- It binds to long chain acyl-CoA by transferase I .(in outer mitochondrial membrane)
  [Acyl-CoA + carnitine $\xrightarrow{\text{transferase I}}$ Acyl-carnitine + CoA.SH]
- Then acyl carnitine enters mitochondrial membrane by aid of translocase enzyme (in inner mitochondrial membrane).
- Inside mitochondria, acyl-CoA is released by transferase II for oxidation, and carnitine carrier gets back to cytoplasm by translocase enzyme to carry more of acyl-CoA.



[Acyl-Carnitine $\xrightarrow[\text{CoASH}]{\text{transferase II}}$ Aceyl-CoA + carnitine].

- Inherited disorder of carnitine deficiency:

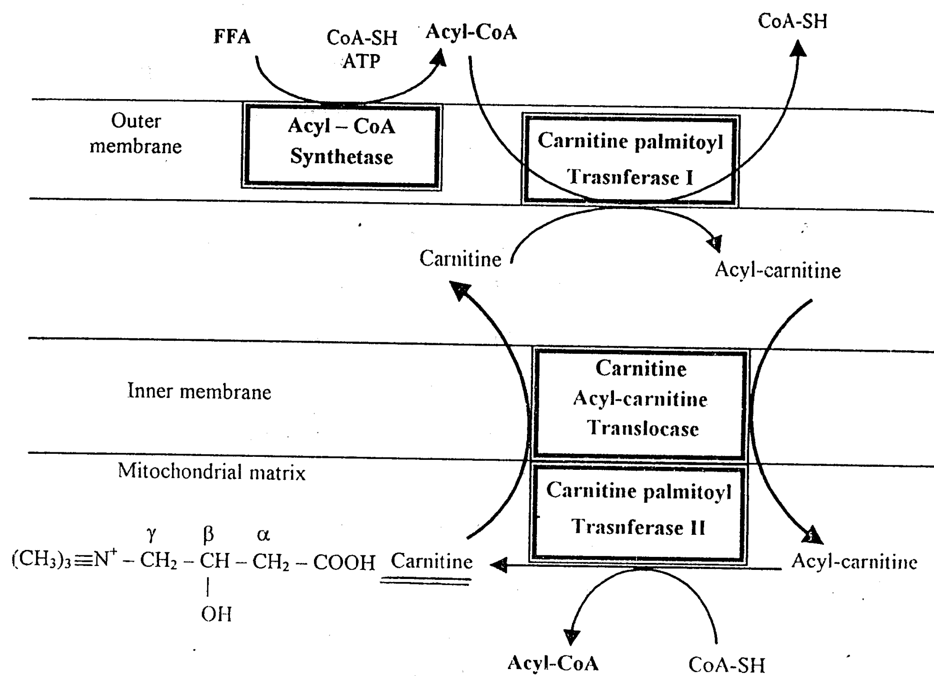
i. In premature infants due to inadequate synthesis.

ii. In adults due to carnitine loss in hemodialysis through the kidneys.

Loss or deficiency of carnitine leads to impaired fatty acid oxidation in mitochondria → muscular weakness.

Also accumulation of fatty acids → increase synthesis of fats → obesity.

Episodes of hypoglycemia may occur due to reduced gluconeogenesis resulting from impaired F.A oxidation (decrease ATP needed for gluconeogensis).



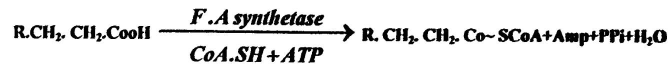
ROLE OF CARNITINE IN THE TRANSPORT OF LONG-CHAIN FA

All these symptoms can be overcomed by oral therapy with carnitine.

- Steps of β. Oxidation:

(1) Activation:

- Fatty acid (palmitate) is first activated in cytoplasm by fatty acid synthetase (thiokinase) enzyme, CoA-SH, and ATP; in which two high energy bonds are utilized.
- The active fatty acid (acyl-CoA) is carried by carnitine to inside mitochondria for oxidation.
- It is the only step which requires two high energy bonds.



$$R.CH_2.CH_2.CooH \xrightarrow[CoA.SH+ATP]{F.A\ synthetase} R.CH_2.CH_2.Co\sim SCoA+Amp+PPi+H_2O$$

(2) Unsaturation:

- Saturated acyl-CoA is converted to unsaturated acyl-CoA by acyl-CoA dehydrogenase and FAD inside the mitochondria.
- Reduced FAD2H is produced which is oxidized in respiratory chain to yield 2 ATP.

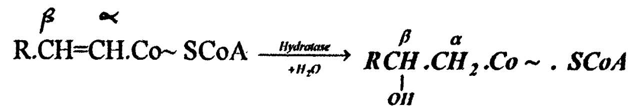


$$R.CH_2.CH_2.Co.SCoA \xrightarrow[FAD]{dehydrogenase} R.CH{=}CH.Co.ScoA + FAD2H$$

Sat. Acyl-CoA Unsat. Acyl-CoA

(3) Hydration:

- Mole of H_2O is added to the unsaturated double bond by enoyl-CoA hydratase, giving rise to β. Hydroxy acyl-CoA.

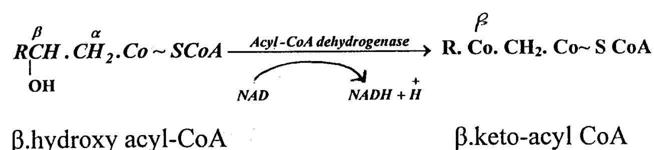


$$\overset{\beta}{R.CH}{=}\overset{\alpha}{CH}.Co\sim SCoA \xrightarrow[+H_2O]{Hydratase} R\underset{OH}{\overset{\beta}{CH}}.\overset{\alpha}{CH_2}.Co\sim.SCoA$$

Unsat. Acyl-CoA β. Hydroxy acyl-CoA

(4) *β.oxidation:*

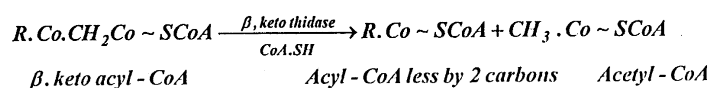
- The hydroxy fatty acid is oxidized at β. Position by removal two hydrogen atoms via β. Hydroxy acyl-CoA dehydrogenase and NAD.
- β.Ketoacyl-CoA is arised in addition to NADH + $\overset{+}{H}$ which yields 3 ATP in respiratory chain.



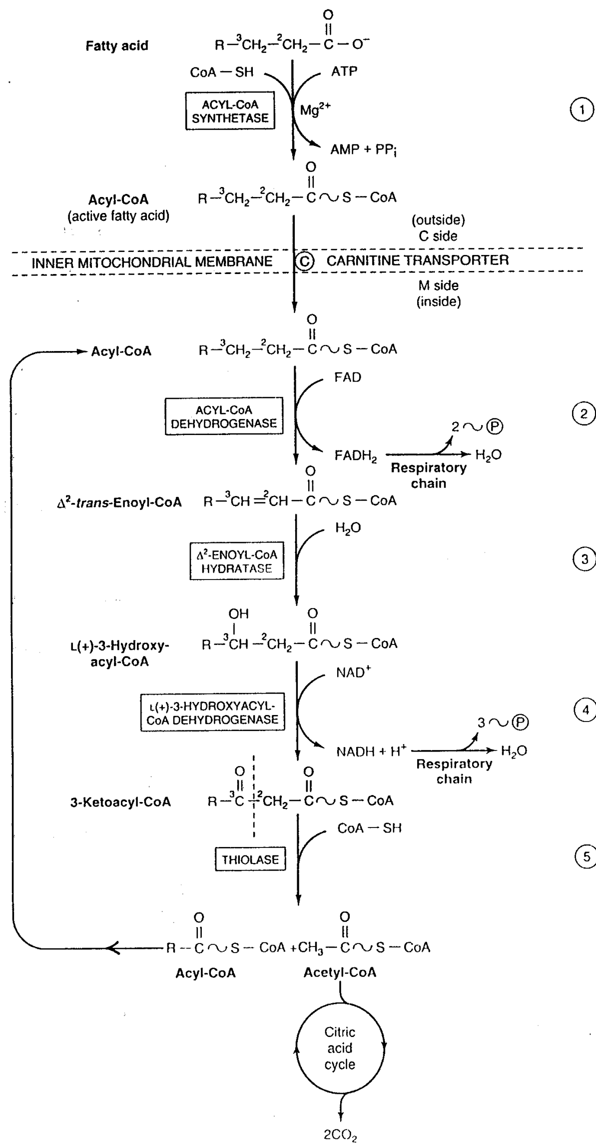
β.hydroxy acyl-CoA β.keto-acyl CoA

(5) *Splitting of two carbons in the form of acetyl-CoA:*

- β. Keto acyl-CoA is splitted from the carboxyl end liberating two carbon atoms in the form of acetyl CoA via β. Ketothiolase and CoA-SH.
- The palmitate fatty acid is now shorter by two carbon atoms than the first one (16C → 14C).
- The separated acetyl CoA is oxidized in citric acid cycle giving rise to 12 ATP.
- The process is repeated seven times until whole fatty acid molecule is converted to aceyl-CoA,. Which is oxidized to yields 12 ATP every cycle.



β. keto acyl - CoA *Acyl - CoA less by 2 carbons* *Acetyl - CoA*



. β-Oxidation of fatty acids. Long-chain acyl-CoA is cycled through reactions 2–5, acetyl-CoA being split off, each cycle, by thiolase (reaction 5). When the acyl radical is only four carbon atoms in length, two acetyl-CoA molecules are formed in reaction 5.

- In the last reaction, acetoacetyl CoA (4 carbons) is formed giving rise to 2 acetyl CoA → 24 ATP.
- Whole palmitate molecule is changed into 8 acetyl CoA & 7 $FADH_2$ & 7 NAD2H
- Oxidation of unsaturated fatty acids (palmitoleic, 16c) gives the same energy of equall carbon atoms of the saturated ones as (palmitate, 16c).
- Oxidation of fatty acids with odd number of carbons, oxidized until 3 carbon atoms (propronyl-CoA) , then converted to succinyl CoA and enter citric acid cycl where it converted to glucose through gluconeogenesis [succinyl-CoA → malate → phospho enol pyruvate → glucose].
- So, inhibition of odd number fatty acid oxidation may lead to inhibition of gluconeogenesis and hypoglycemic attacks (impaired F.A oxid → hypoglycemia).
- Succinyl-CoA, may enter in heme formation.
- Energetics of fatty acid oxidation (palmitate):-

i) Complete oxidation of palmitate (16c) requires 7 times to produce:

- 7 moles of FAD2H, in resp. chain: 7 x 2 = 14 ATP
- 7 moles of NADH + H, in resp. chain: 7 x 3 = 21 ATP
- 8 moles of Acetyl CoA in citriccycle = 8 x 12 = 96 ATP
- Total = 131 ATP.
- There is 2 ATP are consumed in activation.
- So, the net = 131-2 = 129 ATP for palmitic acid-oxidation.

ii) Complete oxidation of stearic acid (18C) requires 8 times oxidations. So, its energetics are: 8 x (2+3) = 40 ATP

- The whole molecule is converted to acetyl CoA [2C] .
- 18 ÷ 2 = 9 acetyl CoA
- 9 x 12 ATP = 108 + 40 = 148 –2 = 146 ATP
- Calculation formula =

$$\left[\left(\tfrac{1}{2}N - 1\right)\times 5\ ATP\right] + \left[\tfrac{1}{2}N \times 12\ ATP\right] - 2\ ATP$$

where N = number of carbons in a fatty acid.

Importance of β. Oxidation:

1. Major source of energy during starvation.
2. Energy source in starvation is about 70% from fatty acids, 20% of body proteins, and 2% liver glycogen.
3. Prefered feul of heart muscle, and skeletal muscles during rest so carnitine is concentrated in this organs .
4. Source of acetyl. CoA → cholesterol , and acetyl choline.
5. Ketone body formation; the last 4 carbon atoms (acetoacetyl CoA) may converted to acetoacetate (Ketone body).
6. Fatty acid oxidation in liver provide most of ATP needed for gluconeogenesis.

Regulation of β. Oxidation:

- Fatty acid oxidation is regulated by ATP moles in the cell, if increase ATP production →inhibition of respiratory chain for FAD2H, NADH, H^+ and vice versa. Also inhibition of citric cycle for acetyl CoA oxidation.

- Hormonal regulation:
  - Insulin inhibits lipolysis and stimulates

Lipogenesis → decreases fatty acid pool → decreases F.A oxidation.

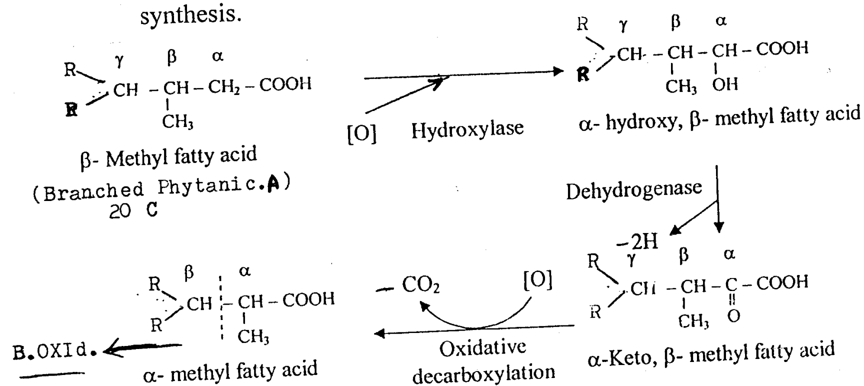
  - Anti-insulin hormones → increase fatty acid oxidation.
- **Efficiency of β. Oxidation:**
  - Energy production of one mole of palmitate β. Oxidation is 129 ATP inside the cell = 129 x 7.6 = 980 KC (every ATP = 7.6 K. calory) as ATP Energy .
  - But complete oxidation in vitro in Bomb calorimeter to one mole palmitate = 2340 K. calory as heat energy .
  - So, the efficiency = $\frac{980}{2340} \times 100$ = 41% of total energy produced inside the body produced as 129 ATP, the remain (59%) is liberated as heat .

II – α –Oxidation of Fatty Acids

- It is minor pathway for fatty acid oxidation in brain tissues, it occurs in cytoplasm microsome.
- It is a mechanism for oxidation of branched chain fatty acids, which are methylated in the β. Position.
- Alpha oxidation is highly specific for phytanic acid (branched, and methylated at β. Position) present in plants or animals eating plants.

Steps:

- There is hydroxylation of β. Methyl fatty acid (phytanic. A) into α. Hydroxy, β. Methyl fatty acid via hydroxylase enzyme.
- Then oxidation by removal of 2 hydrogens from α. Carbon atom via dehydrogenase, and α. Keto . β. Methyl. F.A. is formed.
- Oxidative decarborylation is carried out on α. Keto. β. Methyl fatty acid liberating one mole of CO_2 from α. Position, and α. Methyl fatty acid is formed, now β. Position is cleared from methyl group, and β. Oxidation is carried out .
- Hydroxylated fatty acid may be source of sphingoliped synthesis.



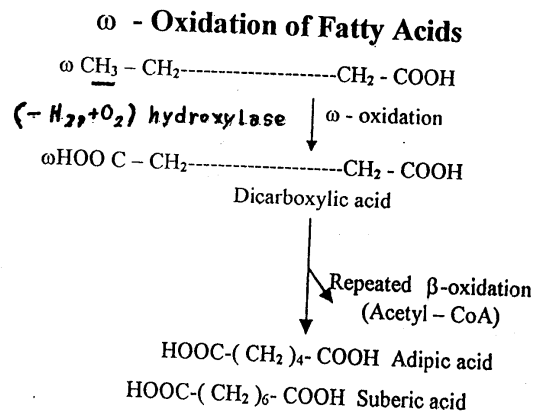
Refsum's disease:

- It is inherited defect in α. Oxidation → phytanic. A accumulation.
- Some food stuffs (vegetables, milk products, animals meet breed on vegetables) contain phytanic acid which is present in phytol of chlorophyll.

- Phytanic acid is toxic branched methylated fatty acid, not oxidized in β. Atom (has CH_3 group) or in α. Atom (genetic defect in its enzymes) → accumulation of phytanic acid → damage to brain cell membrane → mental retardness, deafness, blindness, ataxia, and polyneuritis).

III – ω. Oxidation of fatty acids

- It is very minor pathway, occurs in terminal methyl group (ω), which is oxidized into carboxylic acid.
- Dicarboxylic acid is formed, which is needed to cell membrane structure, no energy is released .
- After formation of dicarboxylic acid, β. Oxidation produces active acetate and last C_6 (adipic acid) or C_8 (suberic acid) are excreted in urine.



LIPOLYSIS

- It is breakdown of stored triacylglycerides (T.G) in adipose tissues.
- T.G in adipose tissues are in balance between lipolysis and re-esterification (formation of new T.G).
- Fatty acids arised from lipolysis carried on plasma albumin protien to different tissues (skeletal muscles, liver, heart, kidney, and lung) for oxidation, where energy supply is required.
- Glycerol is diffused to liver and kidney where it is activated by glycerokinase to glycerol 3-p (adipose tissues are deficient in glycerokinase).
- Excess free fatty acids are re-esterified into new T.G.

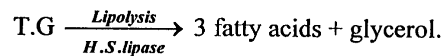
Causes of excessive lipolysis:

In conditions where energy need are required:

- Starvation.
- Diabetes mellitus.
- During growth for anabolism and low carbohydrate diet.
- Chronic infection as T.B due to increase catabolism .
- Heavy smokers (nicotine), coffee drinking (caffaiene), and emotion stress.

Mechanism of lipolysis:

- It starts by effect of anti-insulin hormones (epinephrine, nor epinephrine, and glucagon) on adenyl cyclase (through activation of G protein) in adipose tissues which activate it.
- Active adenyl cyclase converts ATP into 3,5 cAmp.
- 3,5 cAMP stimulates inactive protein kinase → active protein kinase.
- Active protein kinase with ATP stimulates inactive hormone sensitive lipase (dephosphorylated) into → active hormone sensitive lipase (phosphorylated).
- Active H.S.lipase (in adipose tissues) acts on T.G:



- Fatty acids are carried on albumin to be oxidized in different tissues, but glycerol diffuses into liver and kidney for activation by glcerokinase into glycerol 3.p or converted to glucose (gluconeogenesis).
- Glycerol needed for re-esterification in adipose tissues is gained from glycolysis of glucose inside adipose cells.

Factors stimulating lipolysis:

Mostly act via stimulation of 3,5 cAMP formation, which in turn stimulates hormone-sensitive lipase.

1. Hormonal factors : anti-insulin hormones
    a. Epinephrine.
    b. Nor epinephrine.

c. Glucagon.
d. Growth hormone.
e. T.SH.
f. ACTH.

2. Methyl xanthines (caffaiene):

- Caffaiene has no effect on 3.5cAMP formation but inhibits phosphodiesterase (destructs formed 3,5cAMP) thus keeping already formed 3,5cAMP undestroyed.
- So, drinking unsweeted coffee (one cup = 100-150 mg caffaiene) stimulates lipolysis and cause prolonged elevation of human plasma fatty acids which may cause cell excitation and tachycardia.

3. Sympathetic nervous system:

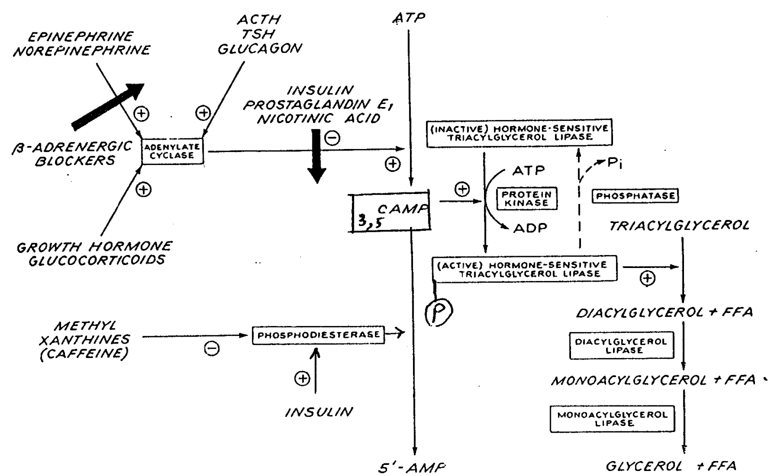
- Nicotine of smoking and prolonged emotion stress may stimulate sympathetic nervous system → increase epinephrine and nor epinephrine → increase lipolysis.

Factors inhibit lipolysis:

1. **Insulin:**

- Insulin inhibits lipolysis by stimulating phosphodiesterase enzyme → increases destruction of 3,5cAMP → decreases lipolysis.
- Also, stuimulates acetyl CoA carboxylase → stimulates lipogenesis.

2. Nicotinic acid (vit B), and prostaglandin E_1:



Control of adipose tissue lipolysis. (TSH, thyroid-stimulating hormone; FFA, free fatty acids.)

- Both inhibit adenyl cyclase → inhibition of 3,5 cAMP formation → inhibition of lipolysis.
- Also, insulin inhibits adenyl cyclase.
- Lipogenesis is inhibited in diabetes tybe 1 but stimulated by obesity.

Types of lipases:

1. Gastric lipase.
2. Pancreatic lipase.
3. Pancreatic phospholipases (A_1, A_2, C and D).
4. Plasma lipoprotien lipase: acts on plasma chylomicrones, and VLDL, it activated by APoCII.
5. Hormone sensitive lipase: in adipose cells, stimulated by adrenaline, glucagon and inhibited by insulin.

LIPOGENESIS

It is capacity of fatty acid synthesis (palimitate), mainly from carbohydrates through acetyl CoA. So, glucose is potentially lipogenic.

Types: is according to type of synthesis:

1. Cytoplasmic (extramitochondrial): is the most common, occurs in cytosol for palmitic acid synthesis; is de-novo fatty acid synthesis.

2. Mitochondrial: for elongation of pre-existing fatty acids in anerobic conditions(absence of oxygen), as in formation of

stearic (18c) from palmitic acid (16c). It utilizes excess of NADPH+H. So , this pathway is active where NADPH + H is produced in excess in anerobic conditions.

3. Microsomal (endoplasmic): for elongation of pre-existing fatty acids (palmitate) into longer chain fatty acids (C_{22}-C_{24}) to form sphingolipids during myelination of CNS, there is utilization of NADPH + H.

4. Saturated fatty acids and mono unsaturated palmito-oliec are synthesized in the body , so if not taken in diet body not suffers.

* Lipogenesis is the reverse of fatty acid B .oxidation

CYTOPLASMIC DE-NOVO SYNTHESIS OF FATTY ACIDS

Definition:

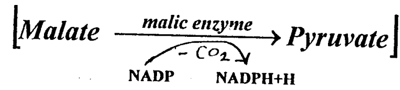
It is capacity of fatty acid synthesis, mainly from carbohydrates through acetyl CoA in cytoplasm.

Site:

In cytosol of liver, adipose tissues, mammary gland, lung, kidney and brain.

Requirements:

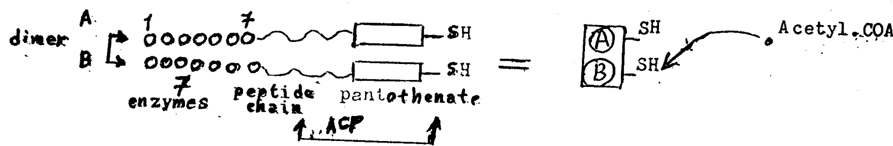
1. Acetyl CoA (is precurser of palmitate) or primary substrate.
2. Reduced NADPH+H from hexose monophosphate shunt, or malate.



3. Fatty acid synthetase complex enzyme:

   It is formed of two monomer subunits (dimmer), every unit contains 7 enzymes required for fatty acid synthesis, and terminal protein named acyl carrier protein (ACP) which carries the acyl coA.

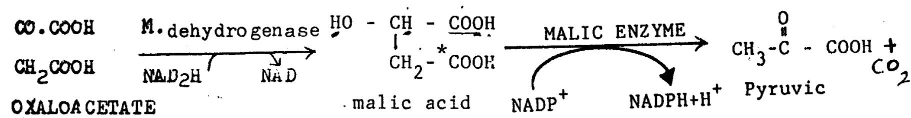
- Acyl carrier protein: is polypeptide chain with pantothenic acid, which have active thiol group (-SH), in which acetyl CoA is attached to it.



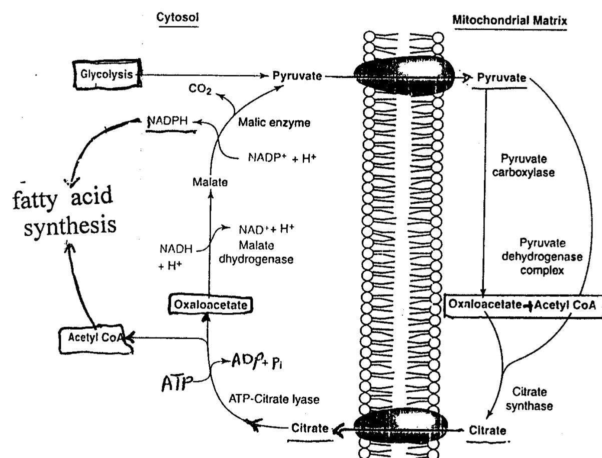
Sources of acetyl CoA:

- Acetyl CoA produced in mitochondria (mainly from glucose oxidation), can't diffuse into cytoplasm for synthesis of palmitic acid.
- Thus acetyl CoA condenses with oxaloacetate to form citrate which is diffusable to cytoplasm by aid with citrate synthase.
- (Acetyl CoA + oxalaocetate $\xrightarrow[synthetase]{citrate}$ citrate + CoA)
- In cytoplasm, citrate is splitted into acetyl CoA and oxaloacetate by aid of ATP-citrate lyase.
- (Citrate $\xrightarrow[CoA,ATP]{citrate\ layse}$ Acetyl CoA + ovaloacetate)

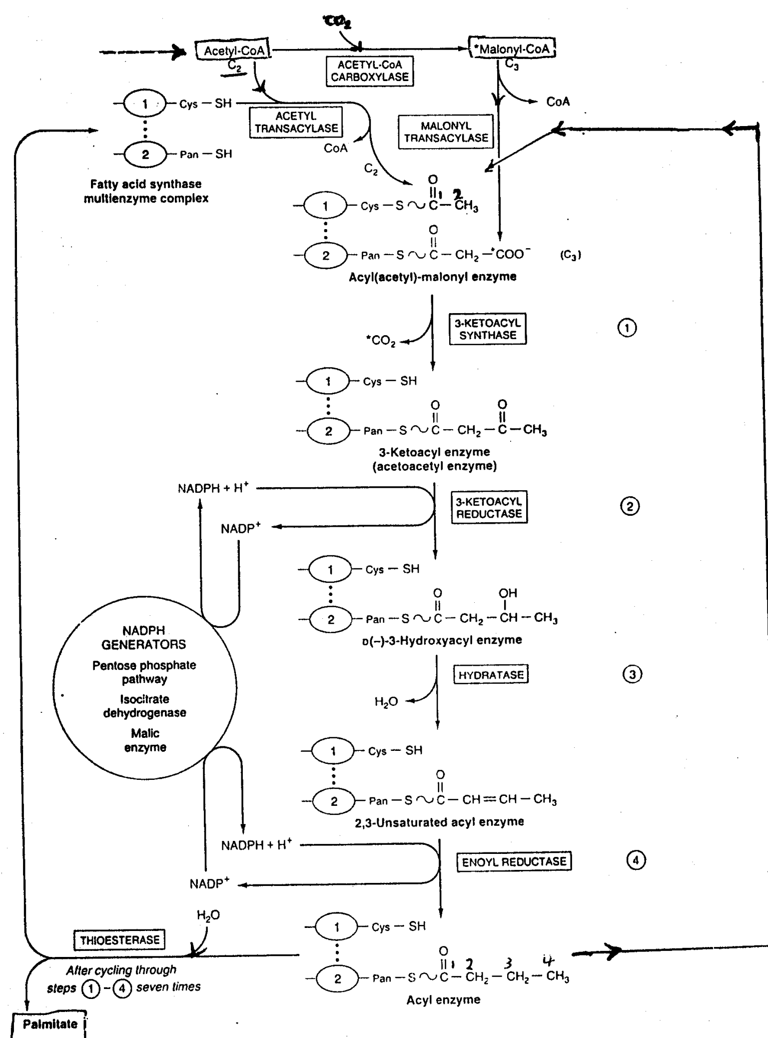
- Oxaloacetate is converted to malate by malate dehydrogenase.
- Then malate is converted to pyruvate and reduced NADPH + H by malic enzymes.



- Formed NADPH +H is utilized for lipogenesis.
- Pyruvate enters mitochondria and converted into acetyl CoA with pyruvate dehydrogenase for further use.



Mechanism for transfer of acetyl CoA from mitochondria to cytosol for fatty acid biosynthesis.

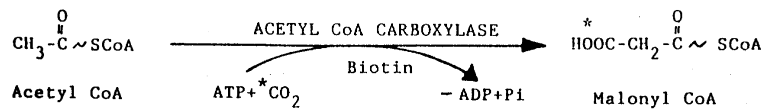


CO_2
Acetyl-CoA
C_2
ACETYL-CoA CARBOXYLASE
*Malonyl-CoA
C_3
CoA
1 Cys — SH
2 Pan — SH
ACETYL TRANSACYLASE
CoA
C_2
MALONYL TRANSACYLASE
Fatty acid synthase multienzyme complex
Acyl(acetyl)-malonyl enzyme
(C_3)
3-KETOACYL SYNTHASE
*CO_2
①
3-Ketoacyl enzyme (acetoacetyl enzyme)
NADPH + H^+
NADP$^+$
3-KETOACYL REDUCTASE
②
D(−)-3-Hydroxyacyl enzyme
HYDRATASE
H_2O
③
NADPH GENERATORS
Pentose phosphate pathway
Isocitrate dehydrogenase
Malic enzyme
2,3-Unsaturated acyl enzyme
ENOYL REDUCTASE
④
H_2O
THIOESTERASE
After cycling through steps ①-④ seven times
Palmitate
Acyl enzyme

Steps of De. Novo palmitic acid synthesis:

1. **Synthesis of malonyl CoA:**

- Malonyl CoA is synthetized from acetyl CoA, CO_2, ATP, and biotin in presence of acetyl CoA carboxylase, is the key enzyme, stimulated by insulin.



2. **Synthesis of palmitate from acetyl CoA:**

- Acetyl CoA reacts with enzyme complex system (ACP) forming acetyl enzyme, through acetyl transferase.
- Malony-CoA reacts with acetyl enzyme forming acetyl-malonyl enzyme through malonyl transferase enzyme.
- The acetyl group condenses with malonyl group (replacing its-CooH), and CO_2 is liberated to form β. keto acyl enzyme through keto acyl transferase thus (SH) group of enzyme complex is freed.
- Then β. keto acyl enzyme is reduced to β. hydroxy acyl enzyme via β. keto acyl reductase, and NADPH + H.
- The β. hydroxy acyl enzyme is dehydrated to unsaturated acyl enzyme by hydratase enzyme.
- Unsaturated acyl enzyme is reduced to saturated acyl enzyme longer than the original by two carbon atoms via unsaturated acyl reductase and NADPH+H.

- The process is repeated 6 times until 16c fatty acid (palmitate) is formed.

The overall reaction for complete synthesis of palmitate:

- Acetyl-CoA + 7 Malonly CoA + 14 NADPH + H → palmitate (16c) + 7 CO_2 + 6 H_2O + 8 CoA ~ SH + 14 NADP.
- Energy utilized :
  7ATP (Acetyl CoA → malonyl CoA) + 14 NADPH + H [Malonyl -CoA → palmitate] .
- Two reduced NADPH+H are utilized every cycle.
  7 + (14 x 3) = 7 + 42 = 49 ATP.

Fate of formed palmitate:

- Esterification with glycerol → T.G , stored in adipose tissues.
- Esterification with cholesterol → cholesterol ester.
- Chain elongation → stearic acid (C_{18}), or by microsomal pathway C_{22-24} for cerebrosides.
- Desaturation of elongated stearic → oleic acid (C_{18}).

Regulation of fatty acid synthesis:

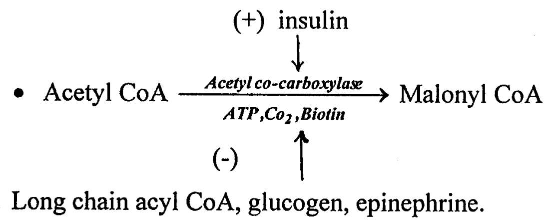
Through the key enzyme acetyl Co-carboxylase.

Stimulation:

Insulin stimulates lipogenesis by induce synthesis and activation of acetyl co-carboxylase.

Inhibition:

- Increased long chain fatty acids (acyl CoA) due to excessive lipolysis lead to inhibition of acetyl – Co-carboxylase → inhibition of lipogenesis.
- Epinephrine and glucogen antagonize action of insulin hormone.



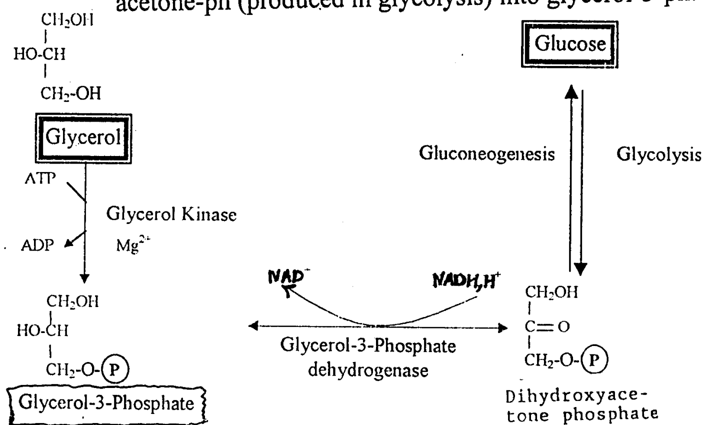
Long chain acyl CoA, glucogen, epinephrine.

SYNTHESIS OF TRIACYLGLYCEROLS

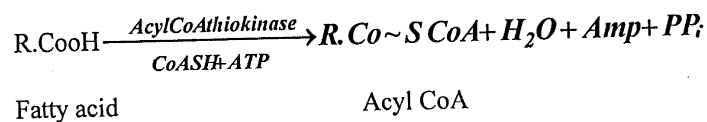
Are formed by combination of activated glycerol-3-ph and three active fatty acids (Acyl CoA).

I – Activation of glycerol to glycerol-3-ph:

- Glycerol is activated to glycerol-3-ph via glycerokinase present in liver, kidney, intestine, and lactating mammary gland.
- In adipose tissues and muscles, glycerokinase is deficient, but glycerol-3-ph dehydrogenase catalyses reduction of dihydroxy acetone-ph (produced in glycolysis) into glycerol-3-ph.



II – Activation of fatty acids:



$$R.CooH \xrightarrow[CoASH + ATP]{AcylCoAthiokinase} R.Co\sim S\,CoA + H_2O + Amp + PP_i$$

Fatty acid — Acyl CoA

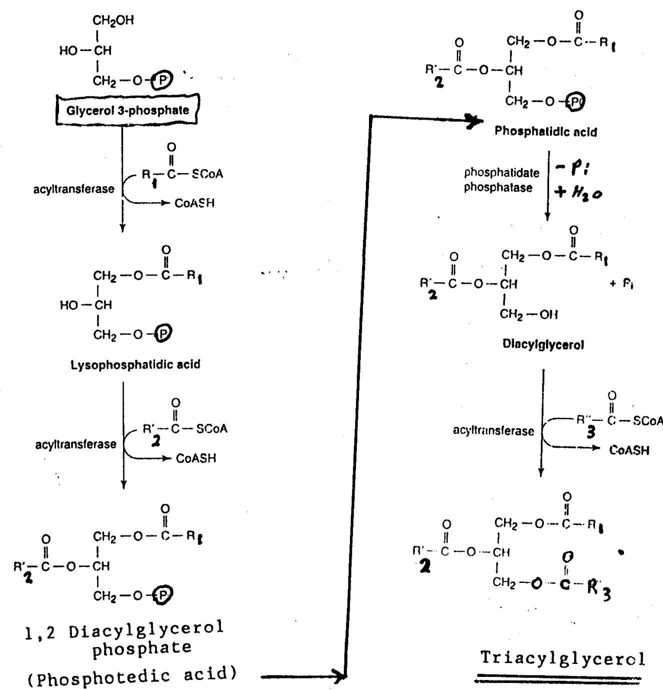
Synthesis of triacylglyceral:

*Two acyl coA (saturated and unsaturated)are added to glycerol 3 ph to form 1,2 diacylglycerol.ph through glycerophosphate acyl transeferase enzyme

*1,2 diacylglycerol-ph is subjected to phosphatase giving rise to 1,2 diacyl glycerol (phosphate group is removed).

*Third acyl CoA is added to form triacylglycerol through diacylglycerol acyl transferase enzyme.

*Most of these enzymes are present in cytoplasm microsomes.



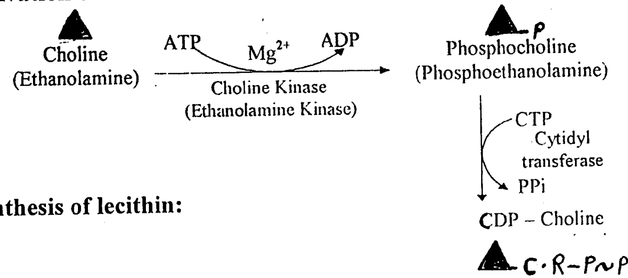
SYNTHESIS OF PHOSPHOLIPIDS

(LECITHIN)

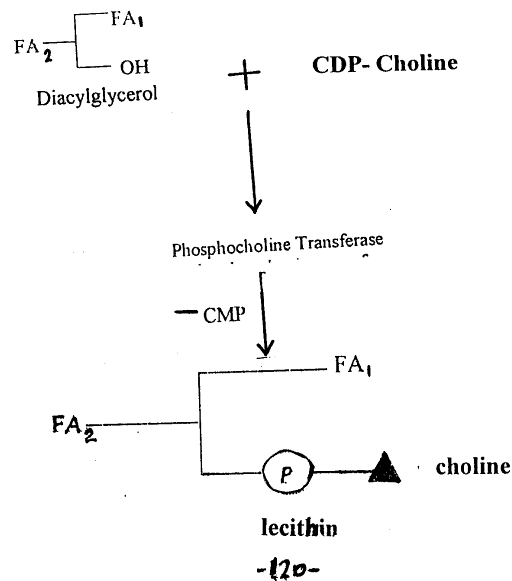
Lecithin is formed of :

Glycerol, 2 fatty acids (sat. and unsaturated), phosphate and choline.

1. **Synthesis of 1,2 diacylglycerol:** as in triacyl glycerol.
2. **Activation of choline into CDP-Choline:**



3. **Synthesis of lecithin:**



FATTY LIVER

Fatty liver is accumulation of abnormal amounts of fat (T.G) about 20-30% of liver weight.

- Liver cells are distended → rupture, and replaced by fibrous tissue (cirrhosis); has no function.
- Normal liver fat is about 5%, mainly as phospholipids (3/4) and triacylglycerol (one fourth).
- About 20% of absorbed fatty acids are normally uptaken by liver cells .

Type-1 overfeeding of fat
Type-2 oversynthesis of fats from carbohydrates
Type-3 over mobilization from depots to liver
Type-4 under mobilization from liver to depots
Type-5 under utilization in the liver.

Causes:

1. Increase synthesis of triacylglycerol in liver:
   a. Excessive fat intake (triacylglycerol) → fatty liver, typeI.
   b. Excessive carbohydrates intake (increased lipogenesis) → fatty liver type II.
   c. Excessive mobilization of depot fat to liver in cases of starvation, diabetes milletus, low carbohydrate diet, and thyrotoxicosis, all due to increased lipolysis → increase free fatty acids in liver → T.G.

   This type of fatty liver is called physiological type III fatty liver.
2. Decrease synthesis and secretion (mobilization) of lipoproteins in liver:
   a. Lipoproteins (as VLDL) help mobilization of fat from liver to peripheral tissues, so decrease apoprotein synthesis(as apoB100)→ pathological fatty liver, type IV.

b. Defiecency of lipotropic factors (choline, methionine, B12,fo;ic acid, betaine, and inositol) specially choline which enters in formation of phospholipids; as constituent of lipoproteins,lipoproteins are required for mobilization of fat from liver to peripheral tissues .

c. Defiecency of essential fatty acids (arachidonic), which enter in formation of phospholipids.

d. Decreased synthesis of apolipoprotein, due to low intake of high biological proteins.

e. Poisoning with heavy metals (lead and arsenic), chloroform and phosphorus inhibit apolipoprotein synthesis in liver → decrease lipoprotein synthesis → fatty liver.

f. Excessive alcohol intake → increases lipogenesis → increase T.G in liver (fatty liver).

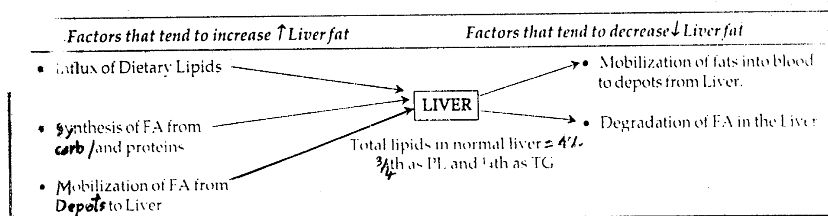
Treatment:

*Low fat diet intake.

*Intake of high biological protein diet (as methionine and phosphoprotien as in casienof skimmed milk)

*Intake of vitamin B .complex and vitamin E(prevent lipid peroxidation)

*Diet rich in essential fatty acids.



PROSTAGLANDINS

They are discovered originally in seminal plasma, now are exist in every mammelian tissues, has potent hormonal like action but act locally.

Prostaglandins are synthetized and inactivated locally in the cell, not stored in any tissues, and rapidly destroyed.

Prostaglandins normalize cell functions, but if produced in excess cause diverse symptoms (pain, cramps, asthma, and inflammation),.

Sources:

Arise from the essential arachidonic fatty acid (20:4).

(1) Diet:

Arachidonic acid, may arise from lenoleic acid (C 18:2) , and α. Linolenic acid (C18,3) in the diet, after removal of (2H) and adding (2C) giving rise to eicosatrienoate, and eicosatetraenoate respictevely.

(2) Cell membrane:

Arachidonic acid may arise also from phospholipids in cell membrane through action of phospholipase A_2 in cell membrane → arachidonic acid + lysolecithin.

Synthesis and types of prostaglandins:

- Arachidonic acid stimulates two enzyme systems in the cell :
  1) Cyclo oxygenase (prostaglandin synthase) and
  2) Lipo oxygenase.
- Arachidonic acid is oxidized and cyclized with aid of cyclo oxygenase and $2O_2$, giving rise to prostaglandin G_2 (PGG_2).

- PGG_2 is converted to PGH_2 via peroxidase enzyme and two reduced glutathiones (2G.SH), and one mole of water is removed.
- PG H_2, is the precursor of other prostaglandins (I_2, E_2, D_2, and F_2) through different enzymatic reactions.
- The number of prostaglandins 1,2,3, ... indicates the number of double bonds present in the prostaglandins.
- Variations in the different groups attached to the prostaglandins ring lead to different types, as E type has keto group at C_9, whereas F types has hydroxyl group in this position.

PGI_2 (prostacyclin):

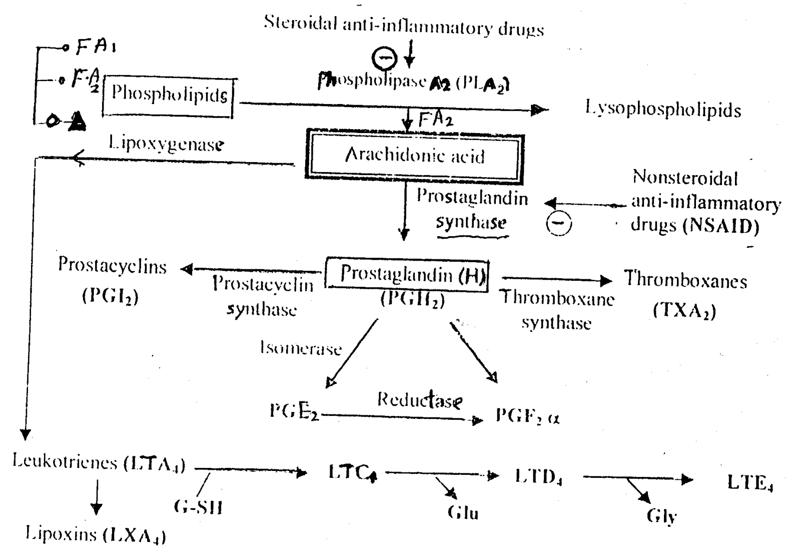
- It arised from PGH_2 via prostacyclin synthase.
- It inhibits platelets aggregation, vasodilator, prevent thrombus.
- It increases formation of camp, produced in blood vessel endothelium.
- Smoking decrease endothelial PGI_2 synthesis → increase platelets aggregation.

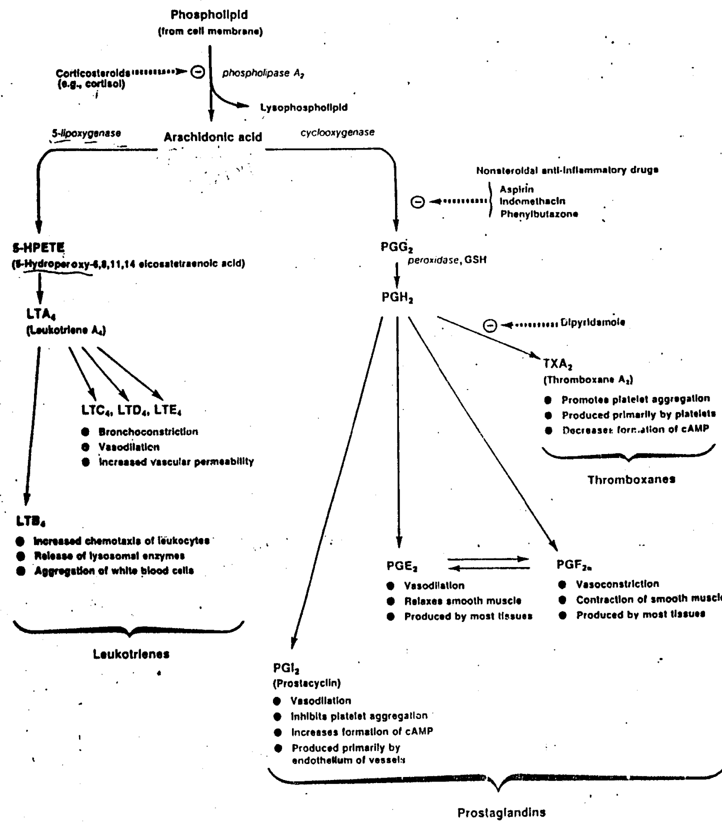
PGE_2:

- Produced by isomerase from PG H_2.
- Relax smooth muscles, vasodilator, produced by most tissues.

PG F_2 α:

- Arised from prostaglandin E_2 via reductase to remove the hydrogen.


Steroidal anti-inflammatory drugs
FA1
FA2
Phospholipids
Phospholipase A2 (PLA2)
Lysophospholipids
FA2
Lipoxygenase
Arachidonic acid
Nonsteroidal
anti-inflammatory
drugs (NSAID)
Prostaglandin
synthase
Prostacyclins
(PGI2)
Prostacyclin
synthase
Prostaglandin (H)
(PGH2)
Thromboxane
synthase
Thromboxanes
(TXA2)
Isomerase
PGE2
Reductase
PGF2 α
Leukotrienes (LTA4)
G-SH
LTC4
LTD4
LTE4
Glu
Gly
Lipoxins (LXA4)


Phospholipid
(from cell membrane)
Corticosteroids
(e.g., cortisol)
phospholipase A_2
Lysophospholipid
5-lipoxygenase
Arachidonic acid
cyclooxygenase
Nonsteroidal anti-inflammatory drugs
Aspirin
Indomethacin
Phenylbutazone
5-HPETE
(5-Hydroperoxy-5,8,11,14 eicosatetraenoic acid)
PGG_2
peroxidase, GSH
PGH_2
Dipyridamole
LTA_4
(Leukotriene A_4)
TXA_2
(Thromboxane A_2)
Promotes platelet aggregation
Produced primarily by platelets
Decreases formation of cAMP
Thromboxanes
LTC_4, LTD_4, LTE_4
Bronchoconstriction
Vasodilation
Increased vascular permeability
LTB_4
Increased chemotaxis of leukocytes
Release of lysosomal enzymes
Aggregation of white blood cells
Leukotrienes
PGE_2
Vasodilation
Relaxes smooth muscle
Produced by most tissues
$PGF_{2\alpha}$
Vasoconstriction
Contraction of smooth muscle
Produced by most tissues
PGI_2
(Prostacyclin)
Vasodilation
Inhibits platelet aggregation
Increases formation of cAMP
Produced primarily by endothelium of vessels
Prostaglandins

- It causes contraction of smooth muscles, so it is present in high content in uterus during labour, but inhibited during pregnancy.
- It is vasoconstrictor, and produced by most tissues.

Thromboxanes (TX):

Thromboxanes are arised from PG H_2, though thromboxane synthase enzyme giving rise to TX A_2 which contains hexa ring (oxane ring) containing oxygen.

- TXA_2 ; is thrombus forming potential and is highly active metabolite, in which by hydration gives rise to inactive TXB_2.
- TXA_2 promotes platelets aggregation, inhibit Camp (in conterary to PG I_2), present mainly in platelets.
- TXA_2 synthase enzyme is abundant in platelets and lung, has very short half life time < 1 minute.
- On the other hand, cyclo oxygenase enzyme is suicide enzyme (autodestructed); once prostaglandin is formed, is rapidly inactivated by prostaglandin dehydrogenase inside the cell.

5. HPETE:

Arachidonic acid is oxidized by other enzyme system called lipo oxygenase, which predominates in neutrophils giving rise to 5.hydroxy peroxy eicosa tetra enoic acid (5. HPETE).

- 5. HPETE, is present also in any organ undergoing an inflammatory response.
- 5. HPETE is converted to leukotriene A_4 via L.T synthetase, with removal of mole of water.

- L.T A_4 is then metabolized either to L.T B_4 by adding water between C_{11}, C_{12} through LTB_4 synthase, or adding glutathione to give rise to L.TC_4 via glutathione transferase.
- Leukotrienes action persist longer than prostaglandins, up to 4 hours.

Biological activities of leukotriens :

1. LTC_4 , LTD_4 and LTE_4:

They comprise the slow reacting substance of anaphylaxis (SRS-A) whose cause contraction of pulmonary air way and gastrointestinal tract.

Also, increase capillary permeability (odema), and vasodilation.

Are potent than histamine 100-1000 times.

2. LT B_4:

- it mediates chemotaxis (migration) of leukocytes, and stimulates adenylate cyclase → increase Camp.
- Aggregates white cells, and release the lysozomal enzymes (antibacterial action).
- It has immunosuppressor action through inhibition CD_4 (T.helper cells) and stimulation of T. suppressor cells (CD_8).
- Immunosuppressor action is worthy in management of graft rejection and autoimmune diseases.
- Antagonists of lipooxygenases and leukotrienes, may used in treatment of asthma, psoriasis, rheumatoid arthritis, and ulcerative colites.

Role of prostaglandins in hemostasis (blood thrombosis and fibrinolysis):

- Blood hemostasis occurs through the time antagonistic prostaglandins: 1) PGI_2 (prostacyclin) and 2) thromboxane A_2.
- PGI_2 (prostacyclin) is produced by the healthy enobthelium of blood vessels.
- It prevents thrombus formation through inhibition of platelets aggregation via stimulating of C.Amp → decrease intracellular calcium → decrease platelets aggregation.
- Thromboxanes A_2 are produced from platelets at damaged endothelium, which cause its aggregation (its release is inhibited by low dose aspirin).
- Therefore, the tendency of platelets to aggregate is determined by the balance between thromboxanes produced by platelets, and PGI_2 produced by endothelial cells.
- So, the low incidence of heart diseases, and diminished platelets aggregation are observed in Greenland Eskimos whose intake much fish oils eicosapentaenoic acid (20:5); ω^3 (timnodonic fatty acid) → increase PGI_2 → decrease platelets aggregation → decrease thrombus formation.
- Also in Eskimos, the plasma choleterol, T.G, and LDL are lowered, while HDL level is increased → decrease otherosclerosis, and cardiac infarction.

Therapeutic uses of prostaglandins:

- Induction of labour at term, termination of pregnancy, prevention of gastric ulcer, control of blood pressure and inflammation, and relief of asthma.

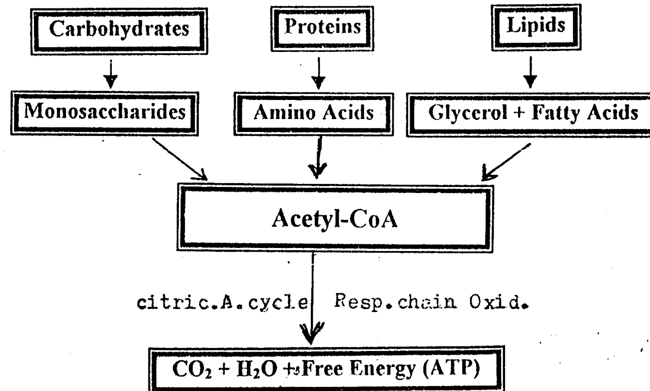
Drugs affect prostaglandin synthesis:

- Epinephrin, and Angiotensin II stimulate phospholipase A_2, while anti-inflammatory corticosteriod inhibit it.
- Aspirin and indomethacin inhibit cyclo-oxygenase enzyme → prevent prostaglandin synthesis.

BIOENERGITICS

Energy is the capacity to do work (mechanical, chemical, or electrical).

Sources of energy :



- Types of human enegy:

1) Free energy:

Is useful energy for body activities (muscular contraction, nerve impulses, active transport and synthesis of compounds), free energy is denoted by delta G, ΔG.

2) Heat energy:

Is to maintain body temperature.

- Biochemical importance:

- Energy extracted from foodstuffs is required for body activities and anabolic processes.
- Depletion of energy reserves may result in death as in starvation.
- Extra energy (surplus) may result in obesity with its complications.
- The rate of energy release is controlled by thyroid hormone.

- Forms of free energy:

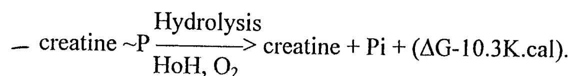
1) Negative(exergonic) free energy: (- ΔG).

In which active compounds in food stuffs intermediates (Ph-Enol pyruvate , NADH+H, cr~p ...) loss energy ~ p to form ATP.

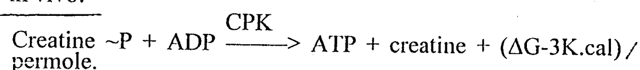
- There is formation (generation) of high energy ATP in respiratory chain or from active compounds by foodstuffs oxidation and loss of that energy to be utilized by other cells.
- The reaction proceeds spontanously in the cell, and is irreversable.

- Examples :

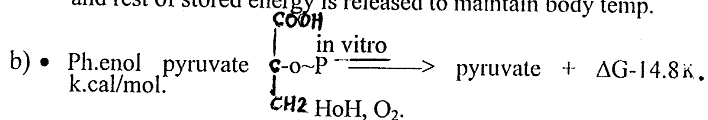
a) • Complete oxidation of creatine ~P in vitro gives rise to -10.3K/cal.



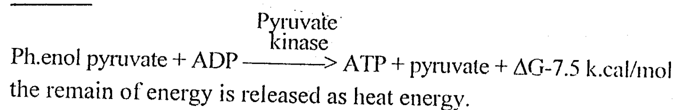
- All energy in creatine ~P is lost as heat energy (-10.3 k.Cal.)
- in vivo:



- Energy stored in cr~P loss about 3K.cal to form ATP, and rest of stored energy is released to maintain body temp.



In vivo:



the remain of energy is released as heat energy.

2) *Positive(endergonic) free energy: (+ ΔG).*

There is gain and utilization of formed energy (ATP) for body activaties, and body anabolic reactions such as glycogenesis, lipogenesis, protein formation, also muscular contractions, nerve impulse, and active

transport in which there is gain and utilization of formed ATP for body activities (as muscle contraction , nerve impulse , and body anabolic reactions as lipogenesis , glycogenesis , and protein synthesis) .

Examples :

a) • Creatine + ATP (A.R-P~P~P) $\xrightarrow{CPK}$ creatine~P+ADD+ (ΔG+1.5k.cal)
OR to form one mole of cr~P, the body utilizes + 1.5 k.cal/.mol from the high energy ATP.

• Creatine gains (utilize) 1.5k.c. from ATP to form cr~p.

• Fructose 1,6 bis-phosphate $\xrightarrow[\text{Split enzyme}]{\text{Aldolase}}$ di-hydroxy acetone-P + glyceraldhyde-3-P + (ΔG + 6 K.cal/mol).

Is the energy in phosphate bond utilized to divide fructose 1,6 – bis-phosphate.

3) Zero free energy (ΔG°):

Is zero standard base line of energy, or the balance between the –ve & +ve free energy in body cells, at pH 7, here the energy is not positive or negative.

ATP – ADP cycle :

Is the process in which high energy ATP phosphate bonds are formed; (exergonic reaction), to be utilized (endergonic) for different body works ,

ATP is converted to ADP which forms ATP again, and so on; or the relationship between ATP generation and its utilization to ADP.

ATP is rapidly consumed and regenerated at very rapid rate (few seconds).

– Sources of ATP formation :

From active compounds of food stuffs oxidation

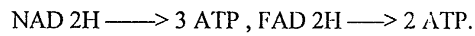
1) Creatine ~P (energy store):



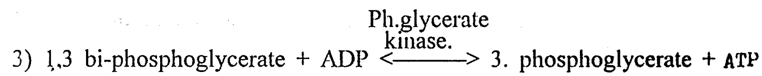
ADP + cr~P $\xleftrightarrow{CPK}$ ATP + creatine.

2) Oxidative phosphorylation (Resp. chain):

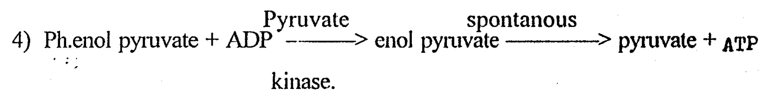
by oxidation of foodstuffs in Resp. chain,:



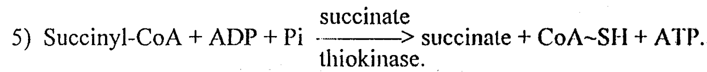
NAD 2H ——> 3 ATP , FAD 2H —> 2 ATP.



3) 1,3 bi-phosphoglycerate + ADP $\xleftrightarrow[]{\text{Ph.glycerate kinase.}}$ 3. phosphoglycerate + ATP

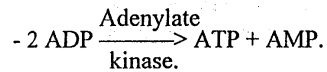


4) Ph.enol pyruvate + ADP $\xrightarrow[\text{kinase.}]{\text{Pyruvate}}$ enol pyruvate $\xrightarrow{\text{spontanous}}$ pyruvate + ATP



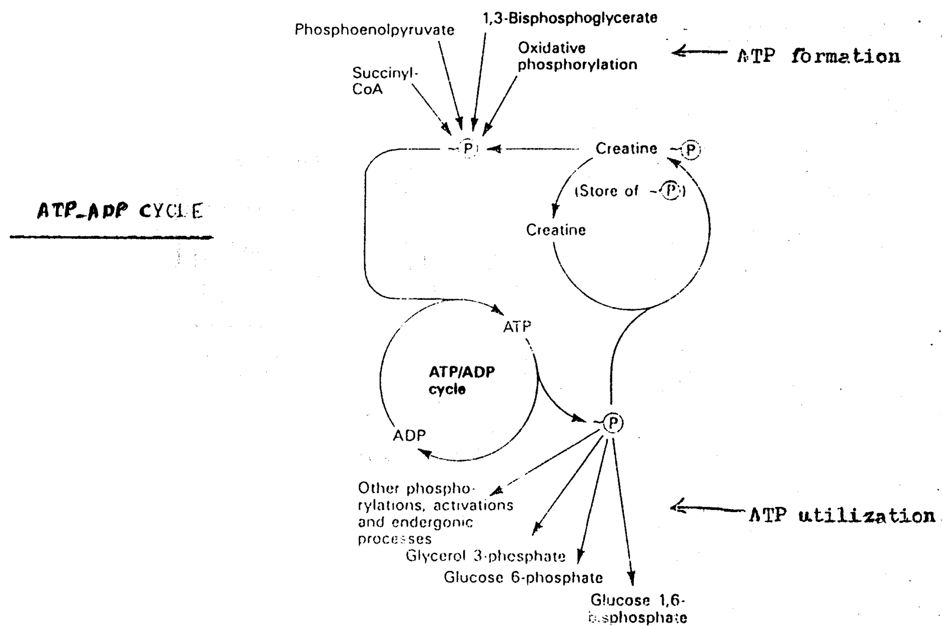
5) Succinyl-CoA + ADP + Pi $\xrightarrow[\text{thiokinase.}]{\text{succinate}}$ succinate + CoA~SH + ATP.

- Also 2 moles of ADP can form one mole of ATP + AMP with aid of adenylate kinase (myokinase) which is present in most cells.



- 2 ADP $\xrightarrow[\text{kinase.}]{\text{Adenylate}}$ ATP + AMP.

ATP-ADP CYCLE



Units of free energy:

1) Ordinary units:

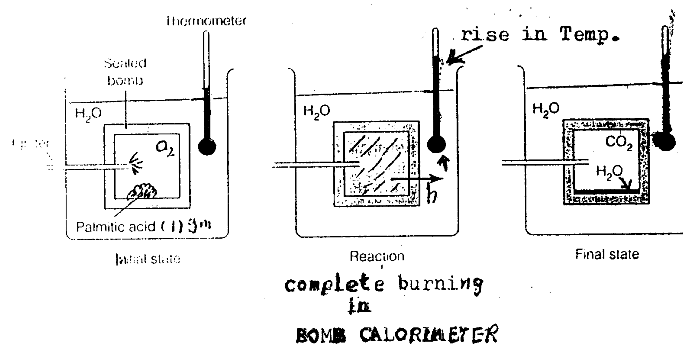
Measured in calories (amount of energy requred to raise one gm of water, by one degree (15C° —> 16C°).

2) SI units:

By joules (one calory = 4.18 joules).

Calculation of calories:

- Calculation of calories in organic compounds is carried out by hydrolysis in Bomb calorimeter:
  - One gram of fat (palmitic acid) or one gram glucose is introduced into sealed bomb calorimeter in presence of oxygen , then complete oxidation is carried out by burning —> energy in fat or glucose is released out as heat which is proportional to its total caloric value.



complete burning in BOMB CALORIMETER

Requirements of bioenergetic system

1) Sources of energy: (Foodstuffs)

Through oxidation of main foodstuffs as carbohydrates, lipids, and proteins ——> acetyl CoA ——> citric acid cycle ——> most of energy.

- Carbohydrates:

1 gm of carbohydrate give rise to 4.1 kilocalor [C] in average, by complete oxidation (burning) in bomb calorimeter (in vitro) in presence of oxygen.

Strarch ——> 4.2 C
Glucose ——> 3.6 C.
} Average 4.1 C

- Lipids:

Fats give rise to 9.3 C

- Proteins:

Amino acids give rise to 4.1 C:

- In body (in vivo) energy is liberated as in bomb calorimeter (presence of oxygen, O_2), but in gradual steps instead of explosive way, in the form of: i) heat (keep body temp.)
  ii) phosphate high energy bonds (ATP).
- No free energy is obtained by breakdown of big organic molecules into smaller ones (glycogen —> glucose-l.ph, T.G.—> glyceral + fatty acids, proteins ——> Amino acids).

2) Oxidation of foodstuffs:

Foodstuffs are oxidized to release energy at:

i) Substrate level (ATP, GTP).

Sources of energy

Standard free energy of hydrolysis of some organophosphates of biochemical importance.

Compound	$\Delta G^{0\prime}$ kJ/mol	$\Delta G^{0\prime}$ kcal/mol
Phosphoenolpyruvate	−61.9	−14.8
Carbamoyl phosphate	−51.4	−12.3
1,3-Bisphosphoglycerate (to 3-phosphoglycerate)	−49.3	−11.8
Creatine phosphate	−43.1	−10.3
ATP → ADP + P_i	−30.5	−7.3
ADP → AMP + P_i	−27.6	−6.6
Pyrophosphate	−27.6	−6.6
Glucose 1-phosphate	−20.9	−5.0
Fructose 6-phosphate	−15.9	−3.8
AMP	−14.2	−3.4
Glucose 6-phosphate	−13.8	−3.3
Glycerol 3-phosphate	−9.2	−2.2

[1]P_i, inorganic orthophosphate.

ii) Respiratory chain level:(reduced NAD —> 3 ATP, reduced FAD → → 2 ATP).

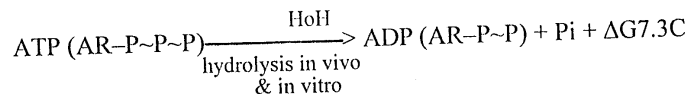
3) Collection & Storage of liberated energy in the form of high energy phosphate bonds:

High energy phosphate bonds give rise to 7-15 kilocalories by complete oxidation (in vitro).

- Forms of high energy phosphate bonds:

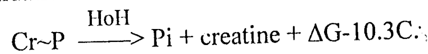
a) ATP:

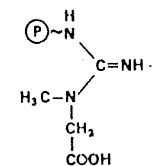
- Is the common currency of energy in the cell (energy donor), where it is present in the form of ATP-Mg^{++} complex as:
  Adenosine (AR)–P ~P ~P —> (ATP).
- ATP has two high energy bonds, each gives about 7.3 C/mol (kilocalory).
- It serves as source of energy for all body works, active transport at cell membranes, activation of glucose, fatty acids, and amino acids.



b) Creatine ~P (energy store):

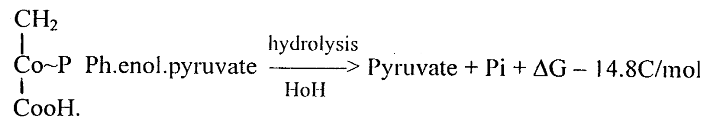
- Any excess of high eneregy phosphate bonds (ATP) are stored in the form of cr~P, its high free energy is about –10.3 k.cal/mol by complete oxidation.



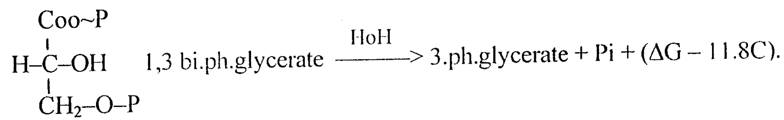


Creatine phosphate

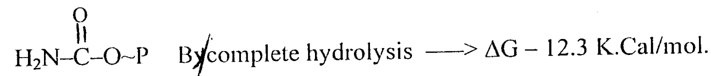
c) <u>Phospho enol pyruvate</u>:



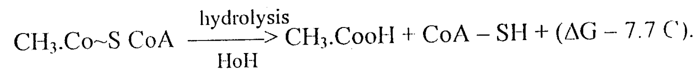
d) <u>1,3 bi.phosphoglycerate</u>:



e) <u>Carbamoyl. phosphate</u>:



f) <u>Thiol-ester bond (acetyl CoA)</u>:



- **<u>Low energy phosphate bonds</u>:** (less than 7 K.cal/mol = smaller than ATP)

a) Glucose-1-ph $\xrightarrow[\text{HoH}]{\text{hydrolysis}}$ ΔG = – 5 K.cal/mol

b) Fractose-6.ph ——> ΔG = – 3.8 K.cal/mol

c) A M P ——> ΔG = – 3.4 K.cal/mol

d) Glucose 6.p ——> ΔG = – 3.3 K.cal/mol

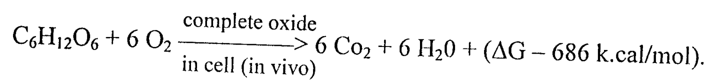
e) Glycerole.3.p ——> ΔG = – 2.2 K.cal/mol

- ADP —> AMP + Pi —> ΔG = – 6.6 K.cal/mol
- Pyrophosphate (PPi) —> ΔG = – 6.6 K.cal/mol

Oxidation of foodstuffs in vivo & in vitro:

- **In vitro:** Oxidation of one gram glucose in bomb calorimeter —> 3.8 – 4.1k. Cal.
- one gm/mol (180gm glucose) X 3.8 for glucose ——In vitro——> 684K.Cal in massive manner not in steps as in vivo, all energy is released as heat .

- **In vivo:** Oxidation of one gram mole glucose in vivo (180gm) gives rise to 686 k.calories (ΔG) in gradual steps. About 42% of this free energy are conserved as 38 ATP, and the remain is released as heat (keep body temp.)



$$C_6H_{12}O_6 + 6\ O_2 \xrightarrow[\text{in cell (in vivo)}]{\text{complete oxide}} 6\ Co_2 + 6\ H_20 + (\Delta G - 686 \text{ k.cal/mol}).$$

[gm/mole glucose = 180gm, equal its molecular weight].

- But oxidation differs in other high energy bonds as cr~P, Ph.enol pyruvte, …

Compound	Mol.mt	In vivo ΔG k.cal/mol	In vitro Caloric value (k.cal/gm)
Glucose	180	– 686	3.8
Palmitate	256	– 2380	9.3
Neutral Fat (Tri-palmitin	809	– 7510	9.3
Lactate	90	– 326	3.6

Respiratory quotient (R.Q):

Is the ratio between O_2 used in oxidation of foodstuff, and Co_2 produced (O_2 is transformed into Co_2)

So, R.Q for glucose = $\frac{6\ Co_2}{6\ O_2} = 1$

R.Q for lipids = $2\ C_{15} H_{110} O_6 + 163\ O_2 \longrightarrow 114\ Co_2 + 110\ H_2O$
(triesterin).

$= \frac{114}{163}$ = 0.7 for lipids.

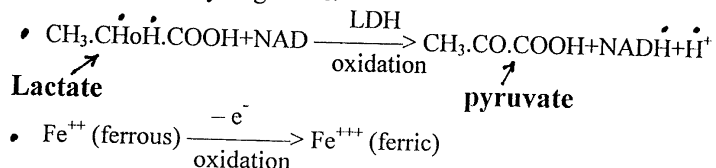
BIOLOGICAL OXIDATION

Biological oxidation means oxidation of food stuffs in the body to liberate energy.

Oxidation is defined as:

1) Addition of oxygen to substrate (is rare in body).

2) Removal of hydrogen or electron from compound (most common in body), with dehydrogenases.



- $CH_3.CHoH.COOH + NAD \xrightarrow[\text{oxidation}]{\text{LDH}} CH_3.CO.COOH + NADH + H^+$

Lactate **pyruvate**

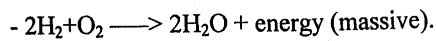
- Fe^{++} (ferrous) $\xrightarrow[\text{oxidation}]{-e^-}$ Fe^{+++} (ferric)

Reduction:

is the reverse of oxidation (removal oxygen, adding hydrogen or electron (+e`).

Redox phenomena:

In common the oxidation reactions are followd by reduction (redex reaction), and are followed by massive liberation of energy.


- $2H_2+O_2 \longrightarrow 2H_2O$ + energy (massive).

Where hydrogen is oxidized, and oxygen is reduced (redox reaction).


- $NADH + H^+ + \frac{1}{2}O_2 \longrightarrow NAD + H_2O$ + massive energy.

- In the living cell, and instead of liberation of massive energy in one step (harmfull to cell), energy is librated in gradual (discrete) steps.
- So that, in every step, only small amount of energy is released (not harmfull to cell).
- This is the difference between stepping out of an upper floor window to reach the ground (traumatic), and going down the stairs (not traumatic).

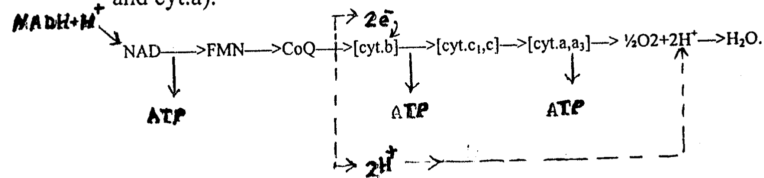
- The released excess energy (ATP) is stored in the form of creatine-phosphate for further use.

RESPIRATORY CHAIN OXIDATION (ELECTRON TRANSPORT CHAIN)

- Respiratory chain oxidation in living cells occures in mitochandria to extract energy from energy rich compounds ($NADH+H^+$, $FADH_2$).
- These compounds arise during oxidation of food stuffs in citric acid cycle, glycolysis and β–oxidation of lipids.
- The reduced substrates ($NADH + H^+$ and FAD2H) contain a pair of hydrogen atoms (2 proten H+, and 2 electrons e`) which passes through the respiratory chain in mitochondria to produce large amounts of energy (ATP) in steps(reduction and oxidation processes followed by release of energy).

- The final reaction is between the two protons (H^+) and respiratory oxygen [O] to yeild one mole of water.

- Components:
  - Respiratory chain consists of 3 hydrogen carriers (NAD, FMN and CoQ) and 3 electron carriers (cytochromes; cyt.b, cyt.c and cyt.a).



OXIDATIVE PHOSPHORYLATION

Is coupling of oxidation with phosphorylation to synthesize ATP in mitochondria.

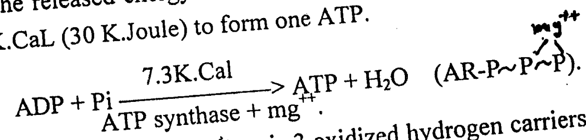
Oxidation:

Means energy released from reduced substrate (NADH + H^+, FAD2H) in respiratory chain.

- Phosphorylation:

- Means coupling of ADP with Pi to form ATP in virtue to the released energy in oxidation reaction.

- The released energy needed to couple ADP to Pi is about 7.3 K.CaL (30 K.Joule) to form one ATP.

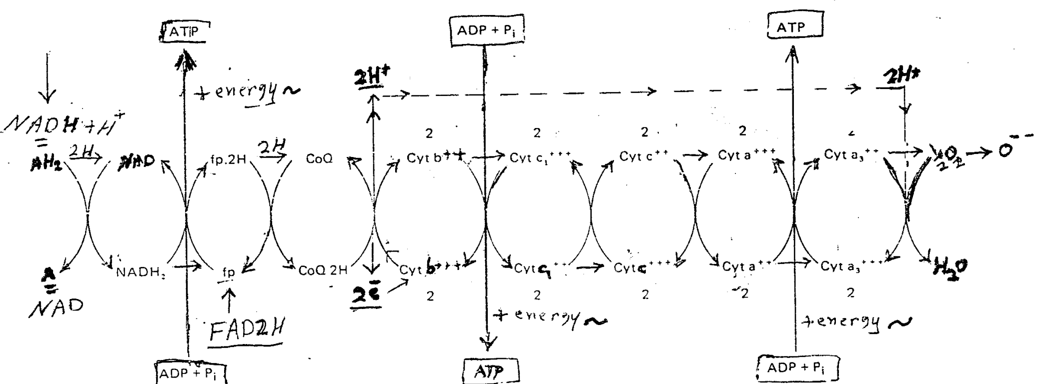


$$ADP + Pi \xrightarrow[\text{ATP synthase + mg}^{++}]{\text{7.3K.Cal}} ATP + H_2O \quad (AR\text{-}P{\sim}P{\sim}P).$$

- In respiratory chain, there is 3 oxidized hydrogen carriers, and 3 oxidized cytochromes (cyt.b.c,a).

- Steps:

- The reduced substrates ($S.H_2$ or $NADH + H^+$) transfer their 2H to the acceptor (oxidized NAD) in respiratory chain, changed it into reduced $NADH + H^+$.
- Then the two hydrogens are removed from $NADH + H^+$ to the flavopratein $FMN \xrightarrow[+\,2H]{\text{reduction}} FMN.2H$
- Then FMN.2H is oxidized into FMN, and the 2 hydrogens are transferred to $Co.Q \xrightarrow[+2H]{\text{reduction}} Co.Q2H$
- During oxidation of FMN.2H → FMN, the first free energy is released to couple with Pi forming first ATP.
- The 2 hydrogen atoms of Co.Q2H are liberated and undergo ionization (dissociation) to give 2 proton (H^+) and 2 electrons (e`).
- The two electrons(2e`) will flow (added) through the cytochromes system (b,c_1,c,a and a_3) to reduce their ferric [Fe^{+++}) ion into the ferrous one (Fe^{++}).
- After reacting with all cytochromes, the 2 electrones react with respiratory $\frac{1}{2} O_2 \xrightarrow{2e^-} O^{--}$ (ionic oxygen).
- The two proton (H^+) arised from Co.Q2H react with ionic oxyten giving rise to H_2O.
- The second ATP is generated in reaction between Cyt.b and Cyt.C_1.



AH_2 = most substrates
NAD = nicotinamide adenine dinucleotide
fp = flavoproteins
Cyt = cytochromes

ATP = adenosine triphosphate
ADP = adenosine diphosphate
P_i = inorganic phosphate

Respiratory chain oxidation
(electron transport chain)

- The third ATP is generated by reaction between Cyt.a and Cyt.a_3. small amounts of energy are released between other steps.
- If reaction begins with reduced FAD 2H instead of reduced NADH + H^+, two ATP is generated only.
- Therefore, one respiratory oxyten atom [O] is reduced by 2 hydrogen protons to H_2O with release of 3 ATP in gradual steps,

  so high phosphate oxygen ratio is 3 for NAD 2H, and P/O ratio

is 2 for FAD 2H.

- Chemistry of respiratory chain components:

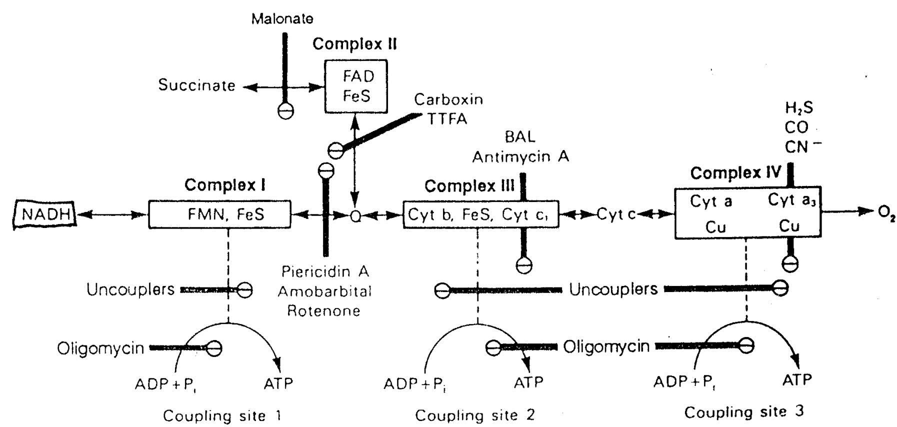
- **Co.Q:**
  - Is hydrogen carrier, links flavoprotein (FMN) to cytochrome system, is related in structure to Vit E, K.
  - Co.Q is also named ubiquinone.

- Cytochromes:

- Are electron carriers, mettaloprotein in nature, has heme ring containing ferric iron (Fe^{+++}).
- The ferric iron ossilates between oxidation and reduction by the two free electrons (e`).
- Cytochrome b, is mettaloprotein containing ferric iron in addition to sulpher.
- Cytochrome a_3, is cytochrome oxidase containing ferric iron in addition to copper.

Uncoupling of phosphorylation:

There is uncoupling of Pi to ADP (oxidation rection proceedes only), so, free energy ATP is not formed, and energy is released in form of heat only in respiratory chain.



Respiratory chain inhibitors

Uncouplers:

Are substances which cause uncoupling of respiratory chain:

1) 2, 4 Dinitrophenol:

Is drug used in obesity, produce sense of heat, and increases the metabolic rate (decrease ATP production) so no extra ATP for lipogenesis is available.

2) Calcium ions:

Calcium ions compete with mg^{++} necessary for ATP activation, so, energy is released in the form of heat.

Therefore calcium I.V injection causes sense of heat.

3) Others:

Thyroxine (increase metabolic rate and heat production), chloro-promazine, oligomycin and progesterone.

- Respiratory chain inhibitors:

They block electron transfer in respiratory chain, but don't cause inhibition of ATP formation.

Block of electron transfer occures at different 3 sites:

- The first:

Prevent oxidation and transfer of substrates between FMN and Co.Q, as barbiturates and rotenone (fish poison).

- The second:

Block electron transfer between Cyt.b and Cyt.c_1, as BAL (antiarsinical) and antimycin. A.

- The third:

- Block electron transfer and also Cyt.a_3, [Cyt.oxidase] as CO, hydrogen sulfide, and cyanide, they totally arrest respiratory chain.

- Cyanide combines with oxidized reduced a_3 (Fe^{+++}) → cyanide–a_3 (Fe^{+++}) complex → rapid inhibition of electron transport → prevent resp. oxygen with reacting with a_3 → stop of mitochondrial respiration → rapid cell death (all body) from tissue asphyxia specially C.N.S.
- If diagnosed rapidly, amyl nitrite I.V. (oxidizing substance) or inhalation can be given to convert oxy.Hb (Fe^{++}) → methemeglobin (Fe^{+++}), which competes with cyanide-a_3(Fe^{+++}) complex to form → cyanide-methemeglobin complex and a_3 (Fe^{+++}) becomes free.
- Then ascorbic acid is given as reducing substance to convert Fe^{+++}. Hb → normal reduced Hb.Fe^{++}.

Control of respiratory chain:

- The coupling of oxidation with phosphorylation is very closed to form ATP.
- If ATP production increases than the cells need, the ADP & pi coupling
  is decreased → inhibition of ATP production (the hydrogen carriers remain in reduced state → prevent receiving of the reduced substrate.
- When ATP is utilized by the cells, the ADP & Pi coupling is increased, allowing the respiratory chain to work again (the hydrogen carriers is in oxidized state allowing receive of the reduced substrates).

- Relation of cardiac ischemia (hypoxia) to cell injury:

- Ischemia of an organ (as heart) affects directly its respiratory chain in mitochondria, leading to slowing or stop of ATP production due to deficiency of oxygen.

- Decrease ATP production leads to failure of active transport of Na^+ pump across cell membrane —> accumulation of intracellular sodium —> water gain —> cell oedema, and may cell rupture.
- Also K^+ diffuses out of the cell → hyperkalemia. Decrease ATP production in the cell → stimulation of phospho- fructokinase (key enzyme in glycolysis) → increase stimulation of anaerobic glycolysis to maintain cell energy → accumulation of lactic acid → decrease intracellular pH → cell dysfunction and lysis → escape of intracellular enzymes to the blood, such as CPK, GOT and LDH, in addition to troponin and myoglobin proteins from the heart muscle.
- All above disorders can be lessened if oxygen is restored → improve mitochondrial function → increase ATP.
- Heart irreversable injury can takes place if ischemia persists to 30-40 minutes (infarction).
- If restore oxygen and ATP, the condition can be improved.

Metabolism of Muscles (cytoskeleton) , and their Biochemical Aspects

- Muscle is the larget single tissue in the human body, makes up about 25% of body mass at birth, more than 40% in the young adult, and less than 30% in the aged adult.

- Type of Muscles :
  I) Skeletal Voluntary Striated muscle.
  II) Cardiac involuntary striated muscle.
  III) Smooth involuntary, non striated muscle.

- Microscopic structure of striated muscles:
  - Muscle fiber is surrounded by plasma membrane called the sarcolemma .
  - Muscle fiber contains a bundle of many myofibrils.
  - Myofibrils are embeded in the intracellular fluid termed sacroplasm which contains glycogen, ATP, creatine~P ,and the glycolytic enzymes.

- Major proteins of striated muscles :

  Fresh muscles are made of 75% water , and 20% proteins ; there is two major proteins (myosin & actin) , and two other minor proteins (tropomyosin & troponins).

  (1) **myosin (contractile protein):**
  Forms about 55% of muscle protein, and forms the thick filaments.

  (2) **Actin (contractile protein):**
  Forms about 25% of muscle protein, and forms The thin filaments .

  - **Thin filament:** is formed from actin , tropomyosin (two stranded protein threads) and the troponin complex protein system which is formed of three subunits polypeptide chains which regulate the muscle contraction.

i) **Troponin – T :**

Which binds to tropomyosin

ii) **Troponin – I :**

Inhibits the actin – myosin interaction → inhibits muscular, contraction

iii) **Troponin – C:**

binds Ca^{++} Which is the key player in muscle contraction, troponin – C is analogue to calmodulin (bounds to 4 molecules of Ca^{++})

- Actin binds to myosin → actomyosin complex, which binds to tropomysin threads in addition to troponon system.
- Proteins of smooth muscle as skeletal , but lacking the troponin system.

- Sequence of Contraction – relaxation of skeletal muscle :

Contraction :-

Motor never impulse to initiate contraction → acetyl choline transmitter at moter end plate → intra cellular Ca^{++} release (4 Ca^{++} moles) → binding to troponin – C → enables myosin to bind with actin → shortening and muscle contraction .

Relaxation :

Ca^{++} is pumped back to sarcoplasm, and also release of Ca^{++} from troponin – C → Stopage interaction between actin and myosin → muscular relaxation.

- Biochemical events during muscle contraction – relaxation:

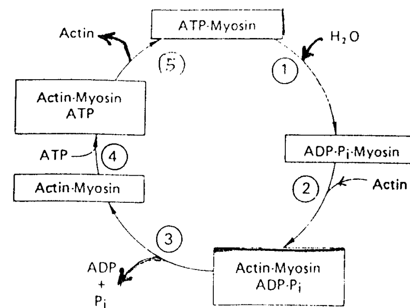
Muscle contraction and relaxation cycle are represented in five steps with aid of ATP.

i) In contraction phase:

- When muscle contraction is stimulated by Ca^{++}, The ATP binds to head of myosin → ATP – myosin
- ATP – myosin binds to actin forming → Actin – myosin – ATP complex with high energy → initiates contraction.
- Then the hydrolysed ATP (ADP+ Pi) is released leaving the actin – myosin in low energy state.

ii) In relaxation Phase :

- Anothen ATP binds to myosin → Actin – myosin – ATP and actin is released out → ATP – myosin in relaxation state.
- Then ATP in myosin is hydrolysed into ADP + Pi (and the released energy is used to bind actin to myosin) and begins another cycle.



The hydrolysis of ATP drives the cyclic association and dissociation of actin and myosin in 5 reactions

- Mechanism of contraction in cardiac muscle:

is similar as in Skeletal muscle, but differs in :-

(1) Extracellular Ca^{++} (Outside Sarcolemma) is required for Cardiac Contraction (intracellular Ca^{++} in Skeletal muscle) , it enters myocytes Via Ca^{++} channels (digitalis used in heart failuse increases myocytes Ca^{++} → increase contraction of heart muscle).

(2) Heart depends upon self intrinsic rhythm (Self generating – Conducting system), not nerve impulse as in skeletal muscle .

(3) Reactions are syncytial between the cardiac myocytes, in skeletal muscle is not syncytium.

(4) Cardiac myocytes has rich blood supply and are condensed with mitochondria than any cell to sustain ATP supply for cardiac contraction.

- Clinical value of troponins:-

- Troponins has isoforms in cardiac and skeletal muscles , in acute myocardial infarction, the cardiac isoforms troponin – T and I are increased in plasma within 2 – 4 hours, its specificity reaches up to 95% for diagnosis.

- Energ Sources of ATP in muscles :

ATP is required as constant energy source for contraction- relaxation cycle in muscles .

(1) **Glycolysis :** of blood glucose or muscle glycogen:

glucose → glucose – 6 – ph → glycolysis (2 ATP) under anerobic conditions during severe muscular exercise.

(2) **Muscle glycogenolysis:**

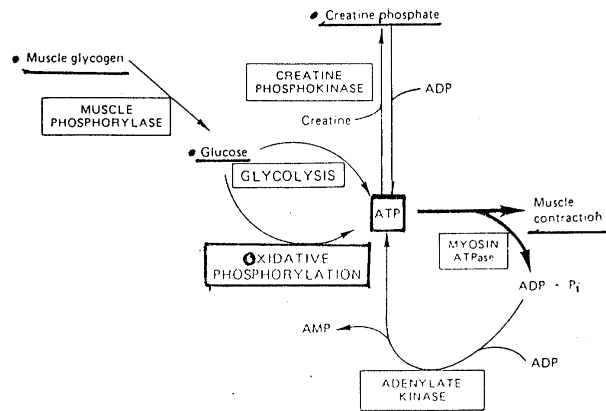
Muscle glycogenolysis $\xrightarrow[\text{Adrenaline + Ca}^{++}]{\text{muscle phosphorylase}}$ glucose – 6 – ph → oxidative phosphorylation, (38 ATP under aerobic conditions during rest, or mild exercise).

(3) creatine – ph hydrolysis in muscles $\xrightarrow[\text{ADP}]{\text{CPK}}$ ATP + creatine.

(4) Two moles of ADP in muscles:

2 ADP $\xrightarrow[\text{Kinase}]{\text{Adenyl}}$ ATP + AMP.

- Then ATP in myosin head of muscle $\xrightarrow{\text{Myosin ATpase}}$ Muscle contraction



Sources of ATP in muscle.

- **Types of skeletal muscle fibers:-**

I) **Slow red fibers** : (Under aerobic condition at rest), Type I.

- Red muscle fibers are suitable for prolonged slow exercise, as in slow contraction for long duration as marathon recing.
- Red muscle fibers has much myoglobin (Supply O_2), and backed with mitochondria, its energy utilization is low, (needs little ATP) has rich blood supply.
- under aerobic condition, muscle gains energy by oxidative phosphorylation from blood glucose (supply energy for about 4 minutis) , Or liver glycogen (18 min), or muscle glycogen (70 min) , or fatty acids (4000 min)
- Therefore, the main feul is muscle glycogen, and fatty acids oxidation in preference to glucose.
- In starvation muscles depend upen ketone bodies to spare glucose for brain and red celds.

II) **Fast white fibers:** (under anerobic conditions in severe exercise, type II

- White fibers are suitable for short rapid Exercise (rapid contraction rate for short duration as in weight lifting and sprinting).
- Muscle fibers has no myoglobin , has few mitochondria, energy utilization is high (needs much ATP)

so under anerobic conditions (as in sprinting and weight lifting) , the major sources of energy are :

i) muscle creatine – ph for first 4-5 seconds.

ii) muscle glycogenolysis for anerobic glycolysis, lactate is formed and is converted to glucose in liver via cori- cycle, accumulation of lactate may cause fatigue.

- Biochemical aspects of contraction – relaxation in smooth muscles –

I) proteins of smooth muscle are :

(1) The contractile myosin, actin, and tropomyosin, but laking the troponin system.

(2) P- light chain myosin : present in sarcoplasm is inhibitory protein , it inhibits actin – myosin interaction. but inhibition of that protein is evoked by phosphorylation → smooth muscle contraction.

(3) myosin kinase :

is protein present in smooth muscle cell , it is activated by the calmodulin – 4 Ca^{++} system.

• then the activated myosin kinase inhibits the P- light chain myosin by phosphorylation in presence of ATP , so it is stimulant of muscle contraction.

(4) Caldesmon protein:

- Present only in smooth muscle, is regulatory protein.
- At low calcium concentration, it binds to actin and prevent actin – myosin interaction , so keep muscle in relaxed state.

II) Contraction – relaxation cycle in smooth muscle :

- contraction phase :

- Nerve impulse or hormonal regulation → release Ca^{++} from extracellular fluid + calmodulin → calmodulin 4.Ca^{++} complex.
- Calmodulin.4Ca^{++} complex + inactive myosin kinas → active calmodulin. Ca^{++}- myosin, which permits actin – myosin interaction → smooth muscle contraction.

- Biochemical bases of procedures that counteract muscle fatigue:

- Fatigue is arised during muscular exercise due to accumulation of lactate and protons (H^+) that decrease the PH of the muscle → affect its function → fatigue

- This can be overcomed by :

(1) **Carbohydrate loading (glycogen unloading- loading):**

- The procedure is popular among long distance runners.
- The player receives very little carbohydrates in diet for three days and performs muscular exercise to depletes the glycogen stores (unloading), then high carbohydrate diet during the last 3 days prior to the race (loading).

(2) **Soda – loading :**

ingestion of sodium bicarbonate to antagonize production of lactate and protons during exercise.

(3) **Oral creatine – Ph:**

Athelets whose perform short duration and high intense efforts as weight lifting. Creatine improves the performance.

(4) **Androstenedione :**

is weak androgen , increases muscle mass and performance.

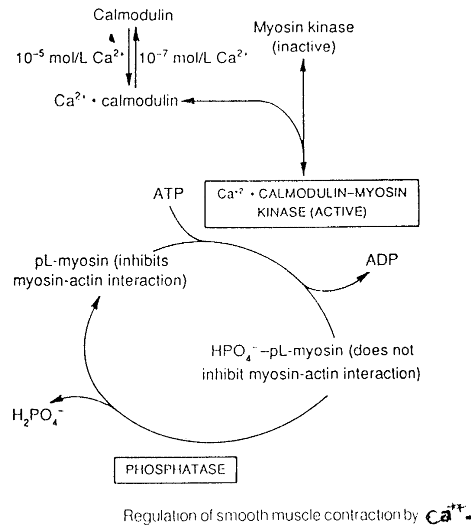
Relaxation phase:

- **Relaxation occures due to:**

(1) Decrease sarcoplasmic Ca^{++} , in which calmodulin – Ca^{++} is not formed, so myosin kinase remains inactive , also at low Ca^{++} the caldesmon protein prevent actin – myosin interaction → smooth muscle relaxation.

(2) Inactivation of myosin kinase.

(3) Dephosphorylation of phosporylated P. light chain by phosphatase enzyme → inhibition of actin – myosin interaction → smooth muscle relaxation.



Regulation of smooth muscle contraction by Ca^{++}.

Smooth muscle regulation

In Blood vessels

- Regulation of smooth muscle tone in blood vessels is due to the endothelium derived relaxing factor [EDRF] , which is stimulated by the gas nitric oxide [NO].

- Now , EDRF was found to be the gas (NO) .

- Elevation of Ca^{++} in endothelial cells loads to liberation of (NO).

- Nitric oxide is originated from argenine , blockage of its formation causes acute elevation of blood pressure.

- The vasodilator nitroglycerine is used in angina pectoris acts by releasing (NO) → Coronary artery relaxation.

  [glycerotrinitrate → in smooth muscle → Nitrate → changed to nitrite → forms NO → Coronary dilatation]

- Synthesis of nitric oxide (NO) :-

i) Endothelial cell :

- Argenine $\xrightarrow[\text{Endothelial } Ca^{++}]{\text{No synthase}}$ Nitric oxide + citrulline.

- Half life time of (NO) is 3-4 seconds.

- the blood vescel vasodilator acetylcholine reacts with the endothelial receptors → relecase Ca^{++} → stimulates NO synthase enzyme → Nitric oxide

- Then (NO) passes to smooth muscle cells.

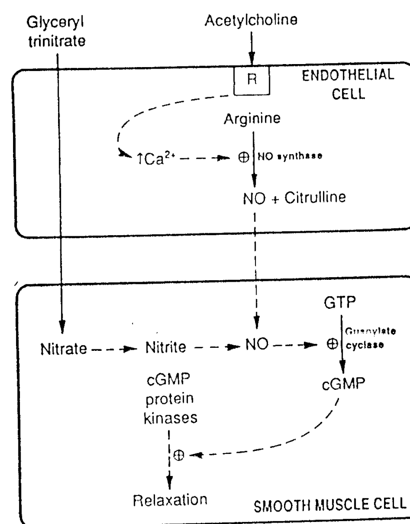


Diagram showing formation in an endothelial cell of nitric oxide (NO) from arginine in a reaction catalyzed by NO synthase.

ii) **in smooth muscle cell:**

- Nitric oxide stimulates guanyl cyclase enzyme which acts on intracellular GTP → cyclic GMP +PPi.
- c GMP. Ph. diesterase inhibits guanyl cyclase → depress muscle relaxation.
- c GMP is inhibitor of platelets aggregation.
- c GMP stimulates GMP protein kinase → relaxation of smooth muscle.
- **Other Functions of nitric oxide:-**

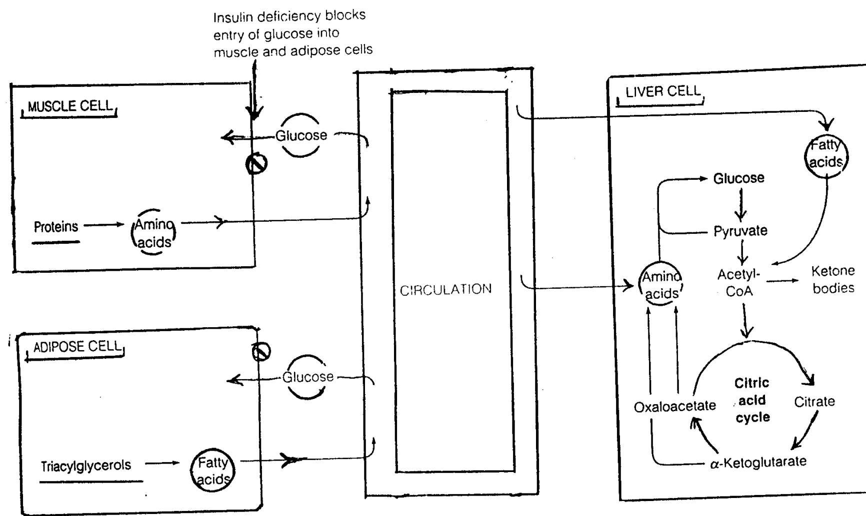
(1) Vasodilator in regulation of blood pressure.

(2) involved in penile erection , sildenafil citrate (Viagra) depresses the inhibitory effect of GMP. Ph. Diesterase , so GMP function is sustained → relaxation of penile vessels → penile erection.

(3) Neurotransmmitor in brain and autonomic peripheral system.

(4) inhibits platelets aggregation.

(5) Low level of nitric oxide may be involved in pylori spasm in infants.



Insulin deficiency blocks entry of glucose into muscle and adipose cells
MUSCLE CELL
Glucose
Proteins
Amino acids
ADIPOSE CELL
Glucose
Triacylglycerols
Fatty acids
CIRCULATION
LIVER CELL
Fatty acids
Glucose
Pyruvate
Amino acids
Acetyl-CoA
Ketone bodies
Citric acid cycle
Oxaloacetate
Citrate
α-Ketoglutarate

Integration of body fuels metabolism during fed and starvation states

Many of the major foodstuffs (Fuels) are interconvertible, such as excess carbohydrates are converted to fatty acids (lipogenesis), and glucogenic amino acids are converted to glucose (gluconeogenesis), that is occurs in normal fed state.

Also excess glucose in fed state can stored as glycogen (glycogenesis).

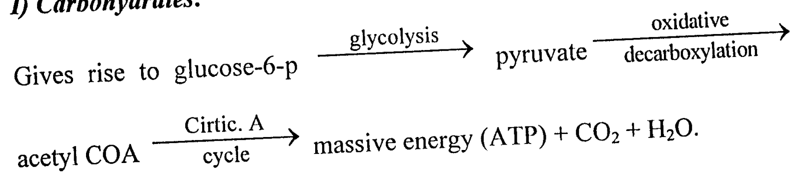
In starvation; free fatty acids, and ketone bodies are oxidized in preference to glucose to spare it for vital organs as heart, and brain which require glucose at all times.

All these processes are controlled by numbers of hormones and enzymes.

Fate of body fuels:

Carbohydrates, lipids, and proteins are the main body fuels

I) Carbohydrates:



Gives rise to glucose-6-p $\xrightarrow{\text{glycolysis}}$ pyruvate $\xrightarrow[\text{decarboxylation}]{\text{oxidative}}$ acetyl COA $\xrightarrow[\text{cycle}]{\text{Cirtic. A}}$ massive energy (ATP) + CO_2 + H_2O.

Excess glucose in fed state can stored as glycogen or fat.

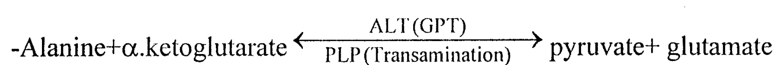
II) Lipids:

Give rise to active fatty acids (cycl-CoA) in which by β-oxidation → acetyl $\xrightarrow[\text{cycle}]{\text{citric. A}}$ CoA energy (ATP)+ CO_2+H_2O.

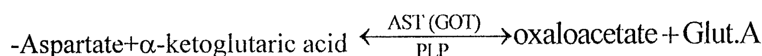
Excess fatty acids can be stored as subcutaneous fat in adipose tissues.

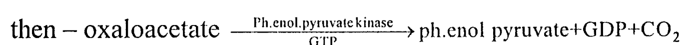
III) Proteins (amino aids):

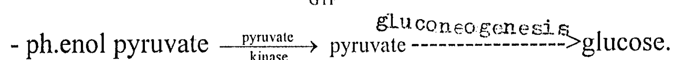
1. Glycogenic amino acids can give rise to pyruvate which in turn is oxidized as glucose → energy in citric acid cycle.


-Alanine+α.ketoglutarate $\xleftrightarrow[\text{PLP (Transamination)}]{\text{ALT (GPT)}}$ pyruvate+ glutamate

- Also, aspartate can give rise to oxaloacetate by transamination, then oxaloacetate is converted into ph.enol pyruvate by gluconeogenesis then ph.enol pyruvate is converted into pyruvate.

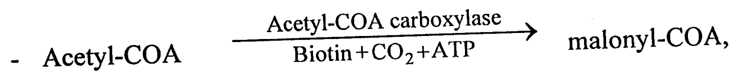

-Aspartate+α-ketoglutaric acid $\xleftrightarrow[\text{PLP}]{\text{AST (GOT)}}$ oxaloacetate + Glut.A


then – oxaloacetate $\xrightarrow[\text{GTP}]{\text{Ph.enol.pyruvate kinase}}$ ph.enol pyruvate+GDP+CO_2

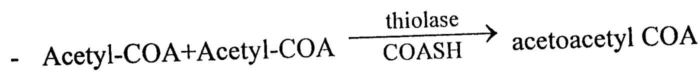

- ph.enol pyruvate $\xrightarrow[\text{kinase}]{\text{pyruvate}}$ pyruvate ---------------gluconeogenesis--->glucose.

2. Ketogenic branched amino acids (isoleucine & leucine) are degraded by transmination gave rise to acetyl-COA during starvation.

- Acetyl-COA is oxidized in citric acid cycle → energy or gives rise to fatty acids and ketone bodies, but can't gives rise to pyruvate or glucose.

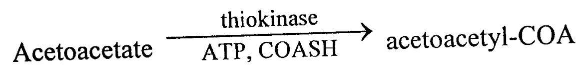
- Acetyl-COA  malonyl-COA,

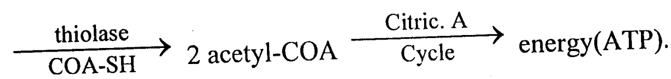
  which is the first step in fatty acid synthesis (in fed state).

- Acetyl-COA+Acetyl-COA  acetoacetyl COA

  which is the first step in ketone body formation via HMG-COA synthase (in starvation state).

- In progressive starvation brain can utilize acetoacetate (ketone body) as energy producer.

Acetoacetate  acetoacetyl-COA



2 acetyl-COA → energy(ATP).

- So ketosis is metabolic adaptation to starvation.

- Brain can't utilize fatty acids (can't pass brain barrier)

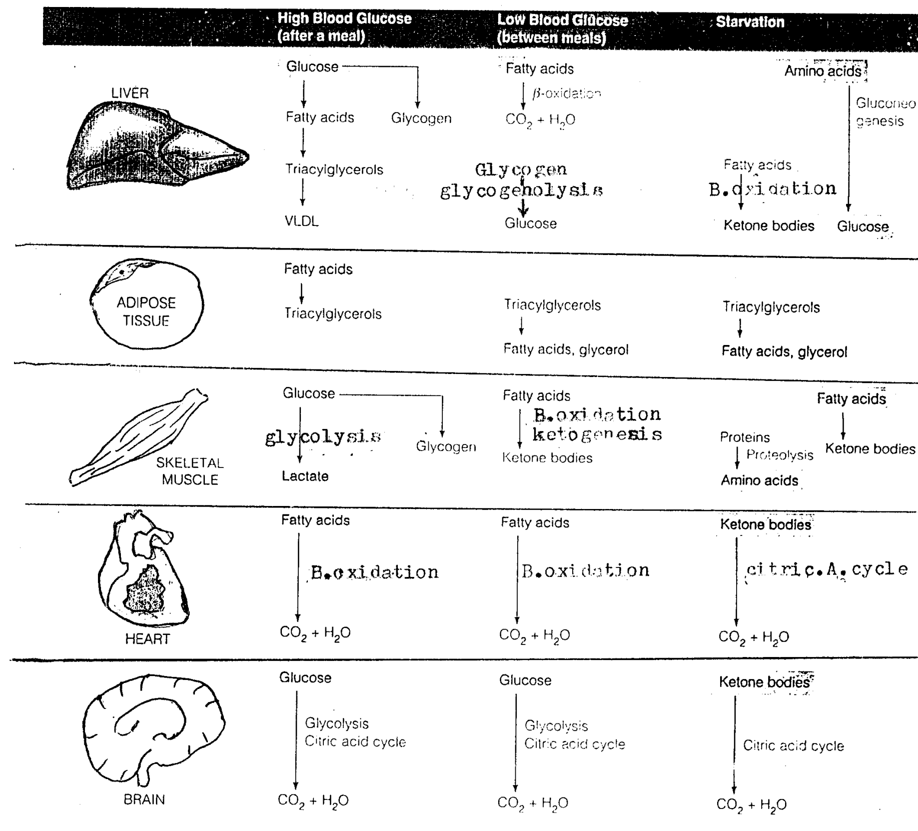
Fuel input and output of major organs in fed and starvation states:

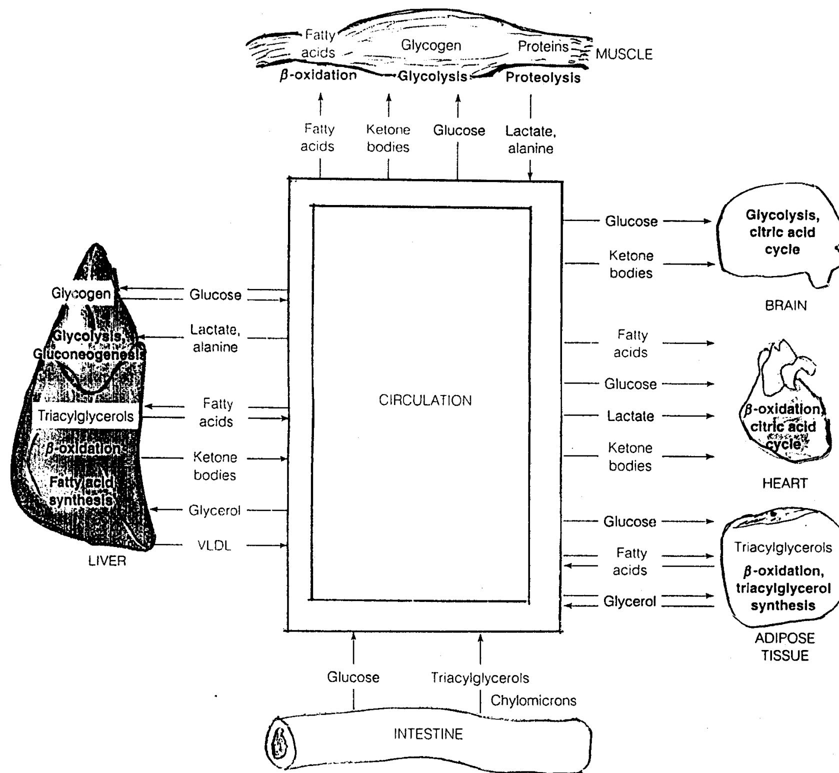
1) Brain:

- In fed state:

Glucose is the preferred fuel, it needs about 120 gm/day which equals 15% of total energy consumed by human.

- Brain needs continuous supply of glucose, because it needs large amounts of energy (ATP) for transmission of nervous impulses to all body.


High Blood Glucose (after a meal)
Low Blood Glucose (between meals)
Starvation
LIVER
Glucose
Fatty acids
Glycogen
Triacylglycerols
VLDL
Fatty acids
β-oxidation
$CO_2 + H_2O$
Glycogen
glycogenolysis
Glucose
Amino acids
Gluconeogenesis
Fatty acids
B.oxidation
Ketone bodies
Glucose
ADIPOSE TISSUE
Fatty acids
Triacylglycerols
Triacylglycerols
Fatty acids, glycerol
Triacylglycerols
Fatty acids, glycerol
SKELETAL MUSCLE
Glucose
glycolysis
Glycogen
Lactate
Fatty acids
B.oxidation
ketogenesis
Ketone bodies
Fatty acids
Proteins
Proteolysis
Ketone bodies
Amino acids
HEART
Fatty acids
B.oxidation
$CO_2 + H_2O$
Fatty acids
B.oxidation
$CO_2 + H_2O$
Ketone bodies
citric.A.cycle
$CO_2 + H_2O$
BRAIN
Glucose
Glycolysis
Citric acid cycle
$CO_2 + H_2O$
Glucose
Glycolysis
Citric acid cycle
$CO_2 + H_2O$
Ketone bodies
Citric acid cycle
$CO_2 + H_2O$


Fatty acids
Glycogen
Proteins
MUSCLE
β-oxidation
Glycolysis
Proteolysis
Fatty acids
Ketone bodies
Glucose
Lactate, alanine
Glucose
Ketone bodies
Glycolysis, citric acid cycle
BRAIN
Glycogen
Glucose
Glycolysis, Gluconeogenesis
Lactate, alanine
Fatty acids
Triacylglycerols
β-oxidation
Fatty acid synthesis
Ketone bodies
Glycerol
VLDL
LIVER
CIRCULATION
Fatty acids
Glucose
Lactate
Ketone bodies
β-oxidation, citric acid cycle
HEART
Glucose
Fatty acids
Glycerol
Triacylglycerols
β-oxidation, triacylglycerol synthesis
ADIPOSE TISSUE
Glucose
Triacylglycerols
Chylomicrons
INTESTINE

- The brain is highly aerobic organ, it utilizes bout 20% of total oxygen consumed by a human.

- ***In starvation:***
- The brain can be adapted to use ketone bodies instead of glucose as major fuel.
- Fatty acids can't be utilized (can't pass brain barrier).

2) Heart:

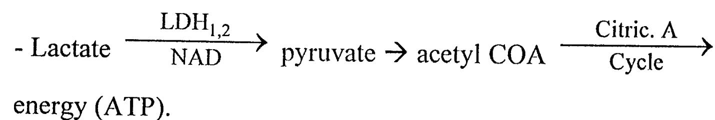
- In fed state:

- The heart is completely aerobic organ, it acts day and night, so needs continuous supply of oxygen and fuels.

- The preferred fuel of heart is fatty acids (via its β.oxidation in mitochondria), so heart contains much mitochondria than any organ (half of the cell is packed with mitochondria).

- In starvation:

- Heart can utilize all fuels; glucose, ketone bodies, and lactate.



- Lactate $\xrightarrow[NAD]{LDH_{1,2}}$ pyruvate → acetyl COA $\xrightarrow[Cycle]{Citric.\ A}$ energy (ATP).

3) Skeletal muscles:

- In rest:

Fatty acids represent the major energy source during muscle resting (ordinary work) to move the muscle bulk.

- ***In exercise:***
- Preferred fuel during muscle exertion is blood glucose, and muscle glycogen which forms about 3/4 of all body glycogen for rapid gain of energy.

- However, glucose-6-p released from muscle glycogen not released to any tissues (due to absence of glucose-6-phosphatase in muscles).

- During muscle excretion (glucose anaerobic oxidation) lactate is formed in muscles (may cause pain or cramps) where it converted in liver to beneficial forms such as:
  i) Glucose: in cori-cycle [2 lactate → 2 pyruvate $\xrightarrow{\text{gluconeogenesis}}$ glycose

  ii) Alanine: is produced in muscle exertion from pyruvate by transamination, where in liver alanine is converted to glucose by gluconeogenesis (alanine-glucose cycle).

4) Liver

- ***In fed state:***
- glucose in liver is converted to glycogen through glycogenesis with stimulation of insulin.

- Excess glucose can give rise to fatty acid synthesis, also with stimulation of insulin, formed triacylglycerol in liver can give rise to VLDL.

- ***In starvation:***
- Liver glycogen is degraded to glucose by glycogenolysis via stimulation of glucagon and epinephrine.
- In starvation, lactate and alanine produced in muscles are converted to glucose in liver (gluconeogenesis) via glucocorticoids.
- Also triacylglycerol in liver is hydrolyzed by hormone sensitive lipase into glycerol and fatty acids which in turn are oxidized to give energy via stimulation of glucagon (stimulates lipolysis).
- Therefore, liver is the site of fuel synthesis for use by other organs, and take major part in fuel integration.

5) Adipose tissues:

- Adipose tissue represents the major fuel depot.
- The total stored triacyglycerols amount is about 135,000 Kcal in average human size, which can sustain life to about 2 months in absence of caloric intake.

- ***In fed state:***
- Triacylglycerols are synthetized in adipocytes (Fat cells) via stimulation of insulin.
- ***In starvation state:***
- Triacylglycerols are broken down to fatty acids and glycerol via stimulation of glucagon.

6) Other body organs:

- Glycolysis occurs only in red blood cells (has no mitochondria), there is gain of 2 ATP per mole of glucose.
- Also glycolysis occurs in other organs where they contain few mitochondria, such as: white cells, medulla of kidney, lens, cornea, and testis.

So, the final oxidation of glucose, fatty acids, ketone bodies is CO_2+H_2O with release of energy via citric acid cycle.

Profiles of the major vertebrate organs in fuel metabolism

Tissue	Fuel Store	Preferred Fuel	Fuel Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (during exertion)	None	Glucose	Lactate, alanine
Heart muscle	None	Fatty acids	None
Adipose tissue	Triacylglycerols	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerols	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

رقم الايداع بدار الكتب
٢٠٠٥/١٤٩١٣
بتاريخ : ٢٠٠٥/٦/٧
الترقيم الدولى: I.S.B.N
977-298-323-0
الناشر : مصر للخدمات العلمية
القاهرة- ٧٣ أ شارع مصر والسودان- حدائق القبة